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Examination of formulation and process factors on the characteristics of fast dissolving and fast disintegrating tablets manufactured by a direct compression process.

Ritesh M. Pabari
Royal College of Surgeons in Ireland, riteshpabari@rcsi.ie

Examination of Formulation and Process Factors on the Characteristics of Fast Dissolving and Fast Disintegrating Tablets Manufactured by a Direct Compression Process

A Thesis submitted to the Royal College of Surgeons in Ireland
for the degree of
Doctor of Philosophy

By

Ritesh M. Pabari B.Pharm, MSc

RCSI
ROYAL COLLEGE OF SURGEONS IN IRELAND
COLÁISTE RÍOGA NA MÁINLEÁ IN ÉIRINN

School of Pharmacy
Royal College of Surgeons in Ireland
123, St. Stephen's Green
Dublin 2, Ireland

Under the supervision of
Dr Zebunnissa Ramtoola, BSc (Pharm.), PhD, M.P.S.I., C.Dip.A.F.(ACCA)

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Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree of Doctor of Philosophy, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed _____

Student Number _____

Date _____

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Presentations, Publications and Patents

Poster presentations

Pabari R., Coughlan B., Sunderland T., Jalal E., Ramtoola Z. Examination of the Effect of Formulation and Process Variables on the Characteristics of Spray Dried Ethylcellulose Microparticles Containing Sodium Diclofenac
Presented at the annual Research Day 11th April, 2007, Royal College of Surgeons in Ireland

Pabari R., Coughlan B., Sunderland T., Jalal E., Ramtoola Z. Examination of the Effect of Formulation and Process Variables on the Characteristics of Spray Dried Ethylcellulose Microparticles Containing Sodium Diclofenac
29th Research Seminar, April 2007 All Ireland Schools of Pharmacy, Royal College of Surgeons in Ireland

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Patents

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Ramtoola, Z., and **Pabari, R.**, Orodispersible dosage forms containing solid drug dispersions, provisional patent application, IE 09395011.2 and US 61/179,061, filed on 18th May 2009, EPO, 25th May 2009

Abbreviations

AAR	Air Aspiration rate
API	Active pharmaceutical ingredient
BC	Biconvex
BP	British Pharmacopoeia
CaS	Calcium silicate
CF	Compression force
CI	Carrs compressibility index
CM	Chocolate + Mint
CS	Crushing strength
DC	Direct compression
DCB	Direct compression base
ρ_b	Bulk density
ρ_t	Tapped density
DFS	Diclofenac sodium
DI	Deionised water
DIT	Drying Inlet Temperature
DL	Drug loading
DSC	Differential scanning calorimetry
DT	Disintegration time of the tablets
D10%	10% of the sample is smaller than this size
D50%	50% of the sample is smaller than this size
D90%	90% of the sample is smaller than this size
EC	Ethylcellulose
EE	Encapsulation efficiency
E100	Eudragit E100
EtOH	Ethanol
FBE	Flat faced bevelled edge
FDDT	Fast disintegrating dissolving tablets

FDT	Fast disintegrating tablets
FFR	Feed flow rate
F-Melt	Fast melt
Friab	Friability of the tablets
FT-IR	Fourier transform infra red spectroscopy
GIT	Gastrointestinal tract
H	Hardness of the tablet
HSM	Hot stage microscopy
IR	Immediate release
K-CLSF	Kollidon CLSF
ludipress	Ludipress®
luquasorb	Luquasorb® 1280
L127	Lutrol 127
MW	Molecular weight
mannogem	Mannogem™ EZ
MCC	Microcrystalline cellulose
M200	Mannitol 200, Parteck® M200
M300	Mannitol 300, Parteck® M300
MgS	Magnesium stearate
min	minute
MP	Melting point
MR	Modified release
NCS	Nozzle cap size
Nl/h	Normliter/hour
NSAID	Non-steroidal Anti-inflammatory drug
ODT	Orally disintegrating tablets
PBS	Phosphate buffered saline
PhEur	European pharmacopoeia
PM	Physical mix
PSD	Particle size distribution
R.H.	Relative humidity

RM	Raspberry + Mint
s	seconds
SD	Spray drying
SDP	Solid dispersions
SEM	Scanning electron microscope
SFR	Spray flow rate during spray drying
SiO2	Silicon dioxide
SIM	Simvastatin
SIM-RS	Simvastatin reference standard
SR	Sustained release
SSG	Sodium starch glycollate (Explotab®)
TDL	Total drug load
TS	Tensile strength
Thick	Thickness of the tablet
Tinlet	Inlet temperature
Toutlet	Outlet temperature
TSC	Total solid content
T20	Tween 20
TGA	Thermogravimetric analysis
Tg	Glass transition temperature
VC	Vanilla + Chocolate
XRPD	X ray powder diffraction
ΔH_{fus}	Ethalpy of fusion

Summary

Oral dosage forms are the safest and most convenient dosage forms and of these tablets are the most popular with patients because of their portability, ease and convenience of dose intake and with manufacturers because of their simple and low cost manufacturing process. Fast disintegrating dissolving tablets (FDDTs), a more recent innovation, have gained a great deal of attention particularly for use in various patient groups such as the paediatric, geriatric, travelling patients and patients having dysphagia. The name "fast-dissolving" indicates that the tablets dissolve fast in the mouth without the aid of water, allowing ease of dose intake by the patients (Banker and Rhodes, 2002).

To meet the goal of fast disintegration in the mouth generally in less than 1 minute, early techniques developed for the production of FDDTs were based on freeze drying or lyophilization (Seager, 1998), molding at low pressure (Makino et al., 1998), sublimation (Koizumi et al., 1997) and tableting followed by humidity and temperature treatment (Mizumoto et al., 1996). A number of these techniques have been commercialized by Cardinal health (Zydis®), Janssen Pharmaceutica (Quicksolv®), Pharmalyoc (Lyoc®), Yamanouchi (Wowtab®). Limitations of these technologies and of the resulting products include complex processing, high cost, tablets with low mechanical strength requiring specialised packaging and low dose content of these tablets.

Subsequently, conventional tableting technologies have been examined and adapted to produce FDDTs. These are based on either granulation or direct compression, and to produce tablets with fast disintegration properties, effervescent excipients and osmotic agents are used and/or tablets are compressed at a low compression force, which results in tablets of low hardness and hence high disintegration properties. Examples of such technologies include Orasolv®, Durasolv® by Cima labs, Advatab® by Eurand.

In the present thesis, a relatively simple direct compression technique was developed in order to prepare FDDTs with high mechanical strength while keeping the attributes of fast disintegration.

To allow for the fast disintegration qualities of the tablets, sugar alcohol based and cellulose based direct compression bases (DCBs) which are either highly water-soluble or water dispersible in combination with one or more disintegrants with differing disintegration mechanism on the mechanical strength and disintegration time of tablets was studied. The addition of hydrophobic and hydrophilic lubricants on the mechanical strength and disintegration characteristics of the tablets was also examined.

The influence of various tableting process variables on the characteristics of the tablets was also studied. Compression force is known to affect the hardness and tensile strength of the tablets as well as the tablet disintegration time (Tye et al., 2004). The influence of increasing compression force from 10 to 20kN on the mechanical strength and DT of the tablets at various tablet diameters, shapes and weights was investigated.

The hardness and tensile strength of tablets formulated using the cellulose based filler, Prosolv® was found to be higher than tablets formulated using the sugar based fillers including sorbitol and Mannitol 200 (M200; mannitol). This was related to the better binding properties of microcrystalline cellulose (MCC) component of the Prosolv filler®. Only Mannitol 200, Prosolv® and sorbitol tablets resulted in tablets which were not friable showing a percent weight loss of less than 1% during the friability test.

The DT of the FDDTs formulated increased in the order of fillers used; mannogem > Mannitol 300 > Prosolv® > Mannitol 200 > Ludipress® > Sorbitol. The lowest DT of 5.67 seconds was observed for Mannogem FDDTs while the highest DT of > 2 minutes was observed for sorbitol.

Tablets containing either Prosolv® or Mannitol 200 (M200) as filler showed a fast DT of below 20 seconds and harder than Ludipress® or any other mannitols therefore were chosen for further study to evaluate the influence of the type of disintegrant on tablet characteristics.

The disintegration time of the tablets was found to be a function of the type of disintegrant used. For tablets containing M200, osmotic agents were found to result in faster disintegration of the tablets, while for tablets formulated with Prosolv®, the superdisintegrants resulted in faster disintegration.

For the M200 based tablets, the disintegration time was found to increase in the order of sodium citrate < calcium silicate < Luquasorb® < Kollidon CLSF < citric acid < SSG. M200 tablets containing SSG produced tablets with the highest disintegration time of 36.67 seconds. On the contrary, for tablets containing Prosolv®, the reverse order of the superdisintegrants was true and can be arranged in the increasing order of DT as SSG < Kollidon CLSF < Luquasorb®. Luquasorb® gave the highest DT of 47.67 seconds for Prosolv® tablets.

The addition of flavours and sweeteners to enhance the palatability of FDDTs at a concentration of 0.5 - 4%w/w or the use of a hydrophilic lubricant did not affect the characteristics of the tablet.

Formulations based on Mannitol 200 or Prosolv® in combination with the superdisintegrants; sodium starch glycollate (SSG), Luquasorb® or Kollidon CLSF (K-CLSF) were found to generate tablets with high tensile strength and low DT in the range of 2 - 49 seconds, hence were selected and applied to the two model drugs. The low DT of 2 seconds was observed for the formulation composition containing Mannitol 200. This was the lowest DT observed or reported for compressed tablets.

The effect of increase in the compression force on the characteristics of the tablets was found to be dependent on the diameter, shape and weight of the tablets. In general, an increase in compression force had a higher effect on the hardness and DT of smaller diameter tablets compared to the larger diameter tablets. Both, the hardness and DT of tablets were directly proportional to the applied compressional force and inversely proportional to tablet diameter for flat faced bevelled (FBE) tablets. For biconvex (BC) tablets, the tablet hardness was proportional to compression force and inversely proportional to the tablet diameter, however, the DT of the BC tablets was found to be independent of the compressional force and tablet diameter.

At similar compressional force, the FBE tablets possessed lower hardness, tensile strength and disintegration time compared to the BC tablets. The disintegration time for the FBE tablets was found to be below 49 seconds, while for the BC tablets the DT was > 1 minute. This was related to the lower hardness and higher porosity of the FBE tablets.

The two model drugs formulated as FDDTs were diclofenac sodium and simvastatin. Both drugs are commercially available as conventional tablets meant to be swallowed with a drink of water. Diclofenac sodium (DFS) is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of pain. FDDT formulations of the DFS would offer a convenient dosage form for the fast relief of pain. In addition, to avoid a multiple dosage regimen, attempts were made to formulate DFS as an FDDT containing modified release microparticles of DFS. Spray drying (SD) was used for the microencapsulation of the DFS using the sustained release ethylcellulose (EC) polymer.

The influence of different spray drying process parameters such as spray flow rate (SFR), feed flow rate (FFR) and air aspirator rate (AAR) on the characteristics of the microparticles showed that a change in the SFR was the most influential factor affecting the particle size, morphology and drug release

characteristics from the microparticles, while FFR influenced the rheology of microparticles. The drug release comprised of an initial burst release of more than 39% in most cases, providing loading dose and subsequent sustained release over 7 hours. DFS release from the ethylcellulose microparticles was characterised by Fickian diffusion.

Diclofenac sodium (DFS) and the microparticles of DFS were used to formulate immediate release and modified release FDDTs, respectively. The use of DFS API showed issues of sticking during tableting which was related to its hydrophobic nature and small particle size of 8.50μm of DFS. In contrast, microparticles of DFS were easily incorporated and formulated as FDDTs. The resultant FDDTs possessed high tensile strength and high porosity, resulting in fast disintegration of the FDDTs. A preclinical palatability study in the canine model showed that the dogs voluntarily accepted the FDDTs, suggesting good palatability of the FDDTs and efficient taste masking of the diclofenac sodium microparticles.

The second model drug investigated was simvastatin, a cholesterol lowering drug particularly used by patients in the 40+ years who most probably are on a range of other medications and are non-compliant with their therapy and hence could benefit from an FDDT formulation. Simvastatin API was formulated using selected mannitol based and Prosolv® based placebo FDDT formulations. FDDTs of low disintegration time of less than 36 seconds and high mechanical strength with hardness in the range of 28.83 to 109.95N were formed. The Prosolv® based FDDTs were found to have higher hardness in the range of 72.28 to 109.95N compared to mannitol based tablets which showed hardness of 28.83 to 54.19N.

However, an increase in tableting speed from 7rpm to 49rpm resulted in tablets with variable weight, hardness and DT. This was related to the hydrophobicity and small particle size of simvastatin resulting in segregation and irregular flow at higher tableting speed.

Two approaches were therefore investigated to improve manufacture of simvastatin FDDTs at higher tableting speed of 49rpm.

(1) To improve rheology and compressibility, simvastatin was first formulated in a matrix of hydrophilic disintegrants by spray drying an aqueous dispersion of the drug and selected disintegrant. The resultant solid dispersions were evaluated for their rheological properties. The formation of such solid dispersions may improve wetting of the drug, resulting in an enhanced dispersibility on contact with aqueous medium and hence dissolution of the drug.

(2) A flow enhancer, colloidal silica (Aerosil®) was added to the formulation as per the conventional industrial technique of improving the rheology of the tablet blend.

Solid dispersions (SDP) formulated using Kollidon CLSF (K-CLSF), sodium starch glycollate (SSG) or calcium silicate (CaS) showed enhanced rheology compared to simvastatin API. This was a result of the greater particle size and uniform particle size distribution. The simvastatin in the SDP was found to be in its crystalline form.

The scalability potential of the simvastatin formulations was examined using mannitol based formulations containing simvastatin-K-CLSF SDP. FDDTs of uniform weight, high hardness and tensile strength of 35.48N and 0.0693N/mm^2, respectively were formed. The DT of the tablets were low in the range of 15.17 to 19.17 seconds. The hardness and tablet tensile strength was lower than the hardness observed at 7rpm which was explained by the decrease in dwell time as the tableting speed increases.

Similarly, mannitol based tablets containing simvastatin API and Aerosil® as a glidant were successfully prepared at both, 7rpm and 49rpm. At 49rpm, the tablets produced were uniform in weight, with hardness of 53.07N and showed low DT of 16.33 seconds. An increase in the compression speed from

7 to 49rpm caused a small decrease in tablet hardness from 54.48 to 53.07N was noted.

Simvastatin FDDTs formulated using a combination of Prosolv® and mannitol with Aerosil® added as a glidant were associated with greater hardness and tensile strength than corresponding mannitol based FDDTs. FDDTs with uniform weight were produced at high tablet turret speed of 49rpm, suggesting good rheology of the formulation blends used. The hardness and tensile strength of the tablets was found to decrease in the order mannitol and Prosolv® 1:1> mannitol 200 and Prosolv® at 3:1> mannitol 200. Addition of Prosolv® to the tablet blend resulted in a decrease in the DT from 16.33 seconds for mannitol 200 based tablets, to 7.17 and 10 seconds for tablets containing a mannitol and Prosolv® in the ratio 3:1 and 1:1, respectively.

The dissolution characteristics of the simvastatin FDDTs formulated at the high speed of 49rpm were compared with the innovator Zocor® tablets. The dissolution of simvastatin from FDDTs prepared using solid dispersion (SDP) of simvastatin was found to be faster in comparison to the FDDTs containing simvastatin API and Aerosil® as a glidant. FDDTs containing SDP of simvastatin were shown to release almost 100% of the simvastatin after 5 minutes. In comparison, 87.05% of the simvastatin released from the FDDTs containing simvastatin API and formulated with Aerosil®. While, 20% of simvastatin was released from Zocor® tablets after 5 minutes. The faster dissolution of simvastatin from the FDDTs may result in faster onset of pharmacological action and has the potential to reduce variability in simvastatin absorption resulting in a simvastatin product with improved and less variable pharmacokinetic profile.

Stability testing carried out on the simvastatin FDDTs produced at 49rpm showed the FDDTs to be stable over a period of 6 months when stored under uncontrolled lab conditions. Negligible changes in mechanical strength, DT, drug content and dissolution characteristics over the 6 months was observed.

Future development of this work would involve investigation of the simvastatin FDDTs in a human pharmacokinetic study to explore its potential for delivering simvastatin with reduced variability. Future work should also investigate the effect of increasing drug content and drug physicochemical properties on (1) the processing of FDDT formulations developed in this thesis and (2) the characteristics of resulting FDDTs to understand the application potential of these FDDT formulations to a wider range of therapeutic areas and higher dose actives.

CHAPTER 1

Introduction

1.0 Introduction

The principal objective of dosage form design is to provide the drug in a suitable form to facilitate handling, aid in delivery of the drug to the blood stream after administration for maximum therapeutic efficacy and to ensure effective clinical presentation. The type of dosage forms designed depend, among other factors, on the drug characteristics as well as the administration route such as oral, rectal, parenteral or respiratory route (Aulton, 2002).

The oral route is the most preferable and frequently used route of administration for most drugs. Compared with other routes it is the simplest, most convenient, safest, noninvasive and practical means of drug administration, and therefore adds to the patient's compliance. It is reported that over 80% of the drugs in the United States are formulated and marketed as oral dosage forms (Banker and Rhodes, 2002). Of these, oral solids and in particular compressed tablets are the most widely used of all pharmaceutical dosage forms (Aulton, 2002; Gennaro, 1990; Lund, 1994).

Tablets represent the cheapest, lightest and most compact of all dosage forms and are the manufacturers' dosage form of choice because of their comparative simplicity, relatively low cost, ease of manufacture and virtual tamper resistance. Tablets have good chemical, physical and microbiological stability and thus have a long shelf life (Aulton, 2002; Banker and Rhodes, 2002; Lachman et al., 1976). Tablets can be made in a variety of shapes and sizes to accommodate various ranges of dose.

The conventional tablet dosage form is designed to be swallowed or chewed for optimum therapeutic effect. However, certain patient populations such as geriatrics, pediatrics and bedridden patients suffering from nausea, emesis and dysphagia have difficulties in swallowing tablets/capsules. For the general patient population, such as patients who are traveling or working and having no access to water, non-compliance with the dosage form becomes an

issue. Improved convenience of a readily administered oral solid would increase patients' compliance with therapy, resulting in enhanced therapeutic efficacy. In recent years fast disintegrating dissolving tablets (FDDTs) have been developed to resolve these issues. An FDDT designed to disintegrate or melt in the mouth without the aid of water, provides ease of administration and dose intake with associated improved compliance with the therapy and disease management. In addition, from the manufacturer's point of view, FDDT imparts unique product differentiation, enabling use as line extensions for existing commercial products.

Fast disintegrating dissolving tablets (FDDTs) also offer other advantages such as (1) rapid absorption resulting in fast onset of pharmacological action upon administration, (2) increased bioavailability of drugs, which are subject to first pass metabolism by facilitating drug absorption across the buccal mucosa. Over the last decade, formulation of FDDTs has received a great deal of attention. Ideally, FDDTs should have the attributes of rapid disintegration and sufficient mechanical strength in order to withstand handling, transport and storage. Significant research has been conducted to investigate the use of various formulations and processing technologies to formulate FDDTs that will satisfy these characteristics. To date, a number of technologies and associated products have been developed and patented by a number of pharmaceutical companies. The technologies or processes used differ and the resulting FDDTs formulations vary in various properties. This review attempts to describe the technologies developed for the preparation of FDDTs, their various formulation and process aspects and related advantages and disadvantages. The impact of formulation and process variables on the mechanical characteristics and disintegration properties of the FDDTs formulated is reviewed and presented below.

Since the FDDTs are designed to melt in the patient's mouth, palatability of the dosage form is vital. A number of sweetening and flavouring agents have been used to mask the taste of the APIs. Another strategy which has been

used is microencapsulation of the API for taste masking. In addition, microencapsulation of API has also been utilised for the preparation of modified release microparticles for inclusion into FDDTs. The various microencapsulation techniques used are also reviewed and presented below.

1.1. Fast Disintegrating Dissolving tablet (FDDT) Technologies

The range of formulation processes studied and developed for the formulation of FDDTs include:

1.1 Freeze drying (Lyophilisation)

1.2 Tablet Molding

1.3 Compaction

- 1.3.1. Tableting based on granulation
- 1.3.2. Tableting based on direct compression

These processes form the basis of various proprietary technologies developed by different pharmaceutical companies and are listed in Table 1.1.

Table 1.1: List of processes and proprietary fast disintegrating dissolving tablet technologies developed

Process	Name of the technology	Company
Lyophilization	Zydis®	Cardinal health
	Quicksolv®	Janssen Pharmaceutica
	Lyoc®	Farmalyoc
	Nanocrystal technology™	Elan
Wet granulation	OraQuick®	KV Pharmaceutical Co
	Frosta®	Akina Inc
	Fast melt®	Elan
Melt granulation	Flashdose®	Fuisz Technologies
Dry granulation	Flashtab®	Prographarm Group
Direct compression based on effervescent formula	OraSolv®*	CIMA labs
	DuraSolv®	CIMA labs
	AdvaTab™	Eurand America
Direct compression at low compressional force	Ziplets®	Eurand Italy
Tableting followed by post-treatment	WOWTAB®	Yamanouchi
Fast disintegrating films	Quick-Dis™	Lavipharm Laboratories

* It was also prepared at low compression force

1.1.1. Freeze drying (Lyophilisation)

Freeze drying (lyophilisation) is a process where frozen water (ice crystals) from a pre-frozen solution or suspension of drug in the presence of a cryopreservative and/or structure forming excipients, is directly sublimed into vapour without passing through melting. The freeze dried product is characterised by a large number of pores due to rapid sublimation of the frozen water and this property was explored for the formulation of fast disintegrating tablets. Three FDDT technologies have already been patented based on lyophilisation and these include Zydis® by R. P. Scherer,

Quicksolv® by Janssen Pharmaceutica and Lyoc® by Farmalyoc, Laboratoires Lafon.

Of these technologies, Zydis® developed by Gregory and Ho, (1981); Gregory et al., (1983); Yarwood et al., (1998), is the first freeze dried technology which has been applied to develop commercial FDDTs, with the first FDDTs commercialised in 1986. Zydis® fast dissolving dosage form is a freeze-dried tablet which when placed into the mouth disintegrates within seconds, rapidly releasing the active ingredient. Due to the highly porous structure of the tablets, the disintegration medium can easily pass through the pores into the core of the tablet, leading to the breakage of inter-particulate bonds and rapid disintegration of the tablet. An example of a commercially available porous fast melt tablet prepared using Zydis® technology is Claritin® RediTabs®, which contains the antihistamine loratadine, Figure 1.1. Electron microscopy of the horizontal cross-section of Claritin® RediTabs®, showing its porous structure is shown in Figure 1.1b.

Figure 1.1: (a) Claritin® RediTabs® final product and (b) SEM of the cross section of a Claritin® RediTab showing the porous nature (Image adapted from Fu et al., 2005).

Using the Zydis® technology, the drug is formulated as solution/suspension in a matrix of water-soluble carrier materials such as mannitol and gelatin. The drug can be incorporated in its original form or as microcapsules. The solution/suspension is then dispensed by weight into preformed pockets of the blister packs and are frozen using a liquid-nitrogen freezing tunnel under carefully controlled conditions to yield frozen units, which have the required structural characteristics. The frozen units are then stored on the refrigerated cabinets before loading into the freeze dryer for final drying by sublimation. The freeze dried units in the blister packs are subsequently sealed with an appropriate covering sheet or laminate. Various sweeteners, flavours and colours can also be added during formulation for enhanced palatability of the fast disintegrating tablets (FDT) (Seager, 1998). Taste masking of the drug was carried out by ion exchange resins, by adsorption of drug.

Carrier materials, such as the sugars used in the Zydis® formulation, impart hardness while polymers such as gelatin, dextran or alginates increase the rigidity and flexibility of the FDDTs. Water is used as the solvent and has the main function of imparting porosity to the matrix, by ice formation during freezing and subsequent sublimation. This porosity is critical to the wetting and disintegration of the matrix. Other excipients which may be added are suspending or flocculating agents for insoluble drugs or a pH adjusting agent to optimise the solubility of the active. A collapse protectant such as glycine is generally included to prevent matrix collapse during freeze drying and storage.

Since the product is freeze dried, it will have low moisture levels to support any microbial growth; however, a preservative may be added. In addition, the entire process takes place at low temperatures, hence, it is suitable for thermo-sensitive drugs.

The overall dissolution rate and hence bioavailability of water-insoluble drugs from the Zydis® dosage form in the fluids of the GIT is reported to be similar

to that from standard oral dosage forms. For water-soluble and ionisable drugs, depending on drug pKa, drug transport through the membranes of the mouth, pharynx and esophagus, is possible and this may result in a faster onset of pharmacological action for drugs. In the case of drugs which are subject to first pass metabolism, an increase in their absorption and bioavailability may be observed (Seager, 1998).

Clarke et al., (2003) studied the absorption of selegiline from the Zydis® formulation. Almost a third of a 10mg selegiline dose in Zydis® Selegiline was absorbed pre-gastrically (predominantly buccally) within 1 minute. The area-under-the curve (AUC) value following the Zydis® 10 mg Selegiline was approximately five times higher than those following conventional selegiline 10 mg tablets. Subsequently, the dose of Zydis® Selegiline was reduced from 10mg to 1.25mg.
When compared with conventional selegiline tablets 10mg, Zydis®, 1.25mg selegiline formulation yielded similar plasma concentrations of selegiline and had a similar effect. The advantage of the lower dose of selegiline is lower concentrations of potentially harmful metabolites, which offer a safer treatment in the management of patients with Parkinson's disease.

The Zydis® technology is one of the most well known technologies, and been applied to different therapeutic classes of actives. Examples of the products currently in the market prepared using Zydis® technology include Zofran®, which contains the antiemetic, ondansetron and is reported to disintegrate in 2.2 seconds and Maxalt® MLT, which contains the antimigraine agent rizatriptan benzoate, and disintegrates in 1.8 seconds (Klancke, 2003; McLaughlin et al., 2009). The composition of Zofran® ODT prepared using Zydis® technology is outlined in Table 1.2 below.

Table 1.2: Examples of marketed preparations prepared by using Zydis® technology and their composition (reproduced from Gad, 2008)

Name (Company)	Examples	Ingredients
Zydis (Cardinal Health)	Claritin Reditab	Micronized loratadine (10mg), citric acid, gelatin, mannitol, mint flavour
Zydis (Cardinal health)	Zofran ODT	Ondansetron (4 or 8mg), aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, strawberry flavor
Zydis (Cardinal Health)	Zyprexa Zydis	Olanzapine (5, 10, 15 or 20mg), gelatin, mannitol, aspartame, methylparaben sodium, propylparaben sodium

The Zydis® technology has some inherent disadvantages such as:

1. It has a limited ability to accommodate high doses of the active. The dose of the drug incorporated in the Zydis® technology is dependent on the aqueous solubility of the drug. The ideal drug candidate for this technology is water insoluble drugs where a dose of up to 400mg may be incorporated. Higher drug doses are reported to reduce the tablet porosity, hence increase the disintegration time (DT). The upper limit for the water-soluble drugs is 60mg, as the dissolved drug might form an amorphous glassy solid on freezing resulting in possible collapse of the tablet on sublimation of ice. A reduction of crystallinity of the matrix results in a reduction of the supporting structure of the matrix.

2. For the water insoluble drugs, the particle size should generally be less than 50μm to prevent sedimentation of the material and formation of a non-homogeneous product. A small particle size is also desirable for a smooth texture and mouth feel.

3. Anticollapse agents are required in the formulation of the Zydis® FDDTs to prevent collapse of the tablet matrix on drying and to provide

additional structure robustness. These include (1) crystal forming excipients to induce crystallinity of the matrix, (2) binding of water-soluble drug on to an ion exchange resin, such as amberlite resins to form a water-insoluble complex.

4. Drugs forming eutectic mixtures cannot be used as these may not adequately freeze to allow appropriate freeze drying to take place. A eutectic mix is a mixture of substances having the lowest freezing point.

5. The drug should be chemically stable in solution over the processing or dose dispensing time of 24 hours at room temperature.

6. Hygroscopicity of the product, which is characteristic of freeze dried products. Zydis® units are sensitive to moisture and would easily pick up moisture from its immediate environment and soften. The Zydis® tablets therefore require blister packaging that is specially designed to protect the formulation from environmental moisture. Minor damages or a pinhole to the blister package can easily lead to softening of the formulation.

7. Due to their high porosity, these FDDTs have an inherent low physical resistance and cannot withstand the push-through pressure required for the tablets packed in conventional blister packs. Therefore, specialised peelable packing foil has to be used for packaging which allows removal of the Zydis units without damaging it (Figure 1.2).

Figure 1.2: Specialized peelable packing foil used for packaging that allows removal of the Zydis® units without damaging it

Quicksolv® technology is another fast dissolving tablet technology that utilizes lyophilisation. This technology was developed and patented by Janssen Pharmaceutica (Beerse, Belgium) (Gole et al., 1993; Gole et al., 1997; Gole et al., 1997b) and is similar to the Zydis® technology using mixtures of amino acids (especially glycine), matrix-forming agents such as gelatin, pectin and mannitol and xanthan gum. In this technology, the porous tablet matrix is prepared by first freezing a solution or suspension of the matrix components in water. A second solvent that is water miscible, usually methanol or acetone, is included at a temperature at which the frozen system is solid. After a few hours in contact with the second solvent, the product is freeze dried resulting in a porous matrix, which disintegrates almost instantly. The addition of the second volatile solvent increases the rate of removal of the water (ice), by forming a low melting point mixture. Compared to the Zydis® method, the Quicksolv® method claims to prevent or reduce the incidence of cracking during the final preparation, resulting in a product with uniform porosity. It also claims to have acceptable mechanical integrity for handling. A requirement of this technology is that the actives should be insoluble in the extraction solvent i.e. the second solvent. A limitation of this technology is that it can be utilised only for low drug content; the maximum dose used in the patent examples was 250mg for Acetaminophen (paracetamol). An example of a commercially

available fast disintegrating tablet prepared by this technology is Propulsid® Quicksolv®, which contains cisapride monohydrate; an aniemetic agent.

The Lyoc® technology developed by Lafon, 1986 (Farmalyoc; Laboratoire L. Lafon, Maisons-Alfort, France) utilises lyophilisation of an oil-in-water emulsion for the preparation of fast disintegrating tablets. The aqueous phase of the emulsion comprises of organic filler(s) and thickening agent(s) constituting from 60 to 85% by weight of the total aqueous phase. The excipients commonly employed are: sugars such as lactose or glucose, sugar alcohols such as mannitol, sorbitol, xylitol, naturally occurring or semi-synthetic polymers such as gelatins and starches, polysaccharides (carrageenin, maltodextrin alginate, dextran); natural gums (acacia and xantham gum); and other polymers such as polyethylene glycol, polyvinylpyrrolidone. The essential lipid component contained in the lipid phase consists of at least one substance selected from the group comprising the triglycerides of (C_8 -C_{18}) fatty acids. An emulsion is first prepared by mixing the liquid lipid phase into the aqueous phase at a temperature within the range of 10°C to 80°C. The emulsion formed is a thickened paste like emulsion that is then dispensed directly in blister pockets that are then prefrozen followed by lyophilisation. The active can be incorporated in its original form or as coated microspheres.

Compared to Zydis® and Quicksolv®, this technology can accommodate high doses of actives without influencing the physical nature of the tablet and hence its in-vitro disintegration time. The thick, paste-like form of the oil in water emulsion helps to prevent sedimentation and hence non-homogeneity in the product. The technology is useful for water sensitive drugs that can be incorporated in the lipid phase. It is also useful for incompatible drugs which can be incorporated separately in the lipid phase and the second active in the aqueous phase. A disadvantage of the product is its low physical strength, a feature of the lyophilisation process.

Lyophilisation has also been used as a process of formulating FDDTs containing small doses of potent actives by Elan (King of Prussia, Pensylvania). In their process, a suspension of nanoparticles at a size below 2μm of the drug, prepared by Elan's Nanocrystal technology™, is formulated in a water-soluble supporting matrix and freeze dried in blisters. A maximum dose of active of 200mg can be formulated. This technology prevents any aerosolized particles from being generated, unlike during conventional dry blending and conventional tableting techniques. The risk of cross-contamination or exposure to hazardous/potent actives is also reduced ensuring safety of the workers. The final product is reported to be sufficiently durable enough to allow use of conventional blister or bottle packaging (Breen, 2006; Fu et al., 2004).

A number of researchers have studied the Zydis® technology by using various actives. Ahmed and Fatahalla, 2007 studied ketoprofen as a model drug and used the Zydis® technology. The drug was dispersed in the solution that contained gelatin. Glycine was added to avoid shrinkage and sorbitol was used to impart crystallinity and hardness to the tablet. The mixture was dosed in the pockets of blister packs, frozen and lyophilized. The saturation solubility and dissolution characteristics of the ketoprofen from porous lyophilized tablet (LT) were three times higher than the unprocessed API. The Lyophilisation process could have led to a decrease in particle size of ketoprofen and its possible conversion into the amorphous form. The lyophilised tablets were physically and chemically stable over a 12 months period at 25°C and 60% relative humidity (R.H.). When compared to the immediate release (IR) ketoprofen conventional tablets, the rate and extent of absorption of ketoprofen from the FDDTs was better, giving an earlier tmax (the time after administration of a drug when the maximum plasma concentration is reached), a higher peak concentration (Cmax), and overall higher bioavailability (AUC).

Chandrasekhar et al., (2009) formulated freeze dried fast disintegrating tablets by a three-stage evaluation process using the Zydis® technology. In stage one, gelatin of various bloom strengths was used individually or in combination and the impact on hardness and DT of the matrix studied. A 5%w/w gelatin formulation comprising of a 50:50 ratio of 75 and 225 bloom strength gelatin (BSGs) was selected for its favourable hardness of 13.7 ± 0.9N and DT of 24.1 ± 0.6 seconds. This formulation was subject to a second stage which involved the addition of the cryoprotectants i.e. saccharides sorbitol, mannitol and sucrose in concentrations between 10% and 80%w/w. Formulations containing Mannitol at 50%w/w showed enhanced hardness of 30.9 ± 2.8N and low DT of 13.3 ± 2.1 seconds. Viscosity-modifying polymers added to this selected formulation were to improve mouth-feel and aid pre-gastric retention. The authors demonstrated that the addition of carbopol 974P-NF resulted in the enhancement of viscosity, however with a compromise of the tablet hardness, whereas Pluronic F127 at 6%w/w showed an increased viscosity with retention of mechanical properties although the DT increased.

Corveleyn and Remon, 1997 investigated the influence of various formulation and process parameters on the characteristics of lyophilised oral dosage forms prepared using Zydis® technology. Hydrochlorothiazide was used as a model drug and matrix forming agents such as maltodextrin were used with xanthan gum or hydroxyethylcellulose (HEC) or hydrolysed gelatin, Solugel® LB was added as binding agent. The resulting tablets were analysed for mechanical strength, porosity and disintegration time. Results showed that the concentration of the maltodextrin and the type of binding agent influenced the characteristics of the tablet. Increasing the concentration of maltodextrin resulted in tablets with high mechanical strength, however pore size and hence disintegration time of the tablets was affected. The DT of the formulations prepared using xanthan gum as a binder was found to be longer, at 55 seconds, compared to the tablets containing hydroxyethylcellulose (HEC) as a binder, which showed a DT of 7 seconds. The in vivo

disintegration time of the tablets containing hydrolysed gelatin Solugel® LB as a binder was below 23 seconds. Unlike the xanthan gum formulations, no gel-like structure formed upon contact with the saliva.

Ahmed and Aboul-Einien, 2007 used the Lyoc® technology to prepare fast disintegrating formulation of griseofulvin (GF) and the influence of formulation parameters on the disintegration and *in vitro* dissolution of GF from lyophilised tablets was investigated. The water phase used was gelatin solution (2%w/v) and medium chain triglycerides (Miglyol) or sesame oil was the oil phase. Different emulsifiers evaluated were Tween 80 and Span 80. All the lyophilised tablets formulated were found to be sufficiently strong for handling. Emulsions containing HPMC as emulsifier showed the highest viscosity while emulsions containing a blend of Tween 80 and Span 80 were less viscous. A formulation consisting Tween 80 / Span 80 as emulsifier disintegrated faster, within 4-5 seconds, compared to the formulation comprising HPMC as emulsifier where the disintegration time was above 2 minutes. This was related to the high viscosity of emulsions comprising HPMC, producing lower porosity tablets after lyophilisation. The use of Miglyol as an oil phase produced tablets with a lower disintegration time of 2.1 minutes compared to the formulation containing sesame oil, at 3.7 minutes.

In vitro dissolution studies showed that lyophilised tablets of GF improved the dissolution rate of the drug compared to the unformulated GF drug. The rate of absorption of GF from the lyophilised tablet was faster than that from the reference tablet and had three times higher peak plasma concentration and shortened time to C_{max} by 4 hours. The extent of absorption, expressed by AUC, was 85% larger compared to the commercial tablet.

The main disadvantage of the lyophilisation process for the preparation of FDTs is the low mechanical strength of the tablets. A general limitation with all freeze-drying processes is the time and careful handling required for processing which together adds to the process cost. In addition, the cost of

the process equipment is high and hence limits the application of this process to actives of high commercial value.

Therefore, attempts were made to replace the freeze-drying step by conventional drying at room temperature or elevated temperature. This led to the development of moulding as a process for preparing fast disintegrating tablets.

1.1.2. Moulding

Moulded tablets are usually produced by using water-soluble ingredients, usually saccharides, to achieve fast disintegration and superior mouthfeel. The tablet mould is prepared by moistening water-soluble materials with water ethanol or hydroalcoholic solvent and compressing the wet mass into mould plates at low compression forces, therefore also known as compression moulding. The solvent is gradually evaporated under standard pressure resulting in the formation of porous tablets. Alternative methods using a solution or suspension of the active in a sugar based matrix followed by drying have also been used.

Many authors have attempted to produce fast disintegrating tablets by using the moulding technique. The various methods mainly vary in terms of the solvent used to prepare the wet mass and the method used to cause evaporation of the solvent resulting in tablets with different characteristics. For instance, Makino et al., (1998) used either water, organic or hydroalcoholic solvent for wet massing and dried the wet mass using a vacuum or jet oven while, Nakamichi et al., (1998) used water as a solvent for wet massing and dried the wet mass at 55°C for 3 hours or at 30°C for 24 hours (Okada et al., 2002).

Makino et al., (1998) (Takeda pharmaceuticals) prepared fast disintegrating tablets by moulding by first producing a wet mass of the drug and a

combination of starches (corn or potato starch) and sugars such as xylitol, maltitol, sucrose or glucose, and other excipients such as citric acid, gelatin, powdered acacia. The solvent used was water, alcohol or hydroalcoholic solution. The mould plates were then dried either in a box type vacuum drier or air dried in a mini jet oven to generate porous tablets of sufficient mechanical integrity. Due to its low drying temperature, this method is useful for heat sensitive actives. The 10mm biconvex moulds possessed relatively lower porosity, higher hardness and higher disintegration time of 24 seconds, in comparison to 20mm flat bevelled edge tablets that showed a DT of 12 seconds.

Nakamichi et al., (1998), (Nippon Shinyaku Kyoto, Japan) prepared compression moulds from a kneaded mixture comprising of a sugar such as xylitol, mannitol, lactose and a binder such as polyvinylpyrrolidone or acacia powder. Water was used to wet mass the various ingredients. The molded tablets were dried at 55°C for 3 hours in a hot air circulation oven to yield fast dissolving tablets. Disintegration of various tablet moulds was found to be below 25 seconds. A formulation consisting a mixture of xylitol and lactose produced tablets with relatively higher DT of 25 seconds compared to the tablets prepared using a combination of xylitol and mannitol (DT=15 seconds).

Humbert-Droz et al., (2000) (Novartis consumer health; Basel, Switzerland) developed fast disintegrating tablets from a suspension or solution of the active drug, a sugar alcohol, PEG 6000, talc, sweeteners and flavors. This was dried by heating, pressure reduction or microwave radiation to give moulded FDDTs which dissolved in the oral cavity in less than 30 seconds.

An alternative method of tablet molding is no-vacuum lyophilization, which involves the evaporation of the solvent using a freezing process followed by vacuum drying. Pebley et al., (1994) (Oregon freeze dry, Albany, USA) reported the formulation of the fast disintegrating tablet matrix by freezing a slurry of the active and excipients at -40°C for 8 hours followed by vacuum

drying for 4 hours above the collapse temperature. The authors reported that a lower porosity of the tablets formed contributed to a disintegration time of greater than 1 minute.

Heat moulding is a technique where the active is dissolved or dispersed in a molten matrix carrier and subjected to drying and cooling at ambient pressure. Van Scoik, 1992 prepared Estazolam FDDT using molten cotton seed oil flakes. The drug was dispersed in the oil and sprayed in a fluid-bed dryer to form droplets that consisted of crystals of estazolam in the hydrogenated cottonseed oil droplet. These droplets solidified on contact with cool air drawn into the fluid bed dryer. To manufacture the tablet triturate, the solidified drug/oil droplets are blended with lactose monohydrate, various flavours and/or sweetening agents, wet massed and molded into FDDTs and dried.

In general, the process of moulding results in poor mechanical strength of the molded tablets with DTs that are below 1 minute. The method may not be applicable to certain actives for example water sensitive or heat sensitive actives. In addition, as for lyophilisation, the process is time and energy consuming.

1.1.3. Compaction

Compaction is the conventional method of producing fast disintegrating tablets and has the advantages of low manufacturing cost and ease of technology transfer. This method has been adapted to prepare fast dissolving tablets and a number of proprietary technologies have been developed and commercialised. Compaction can be further sub-categorised depending on the processing steps involved as, Tableting based on granulation methods and Tableting based on direct compression

1.1.3.1. Tableting based on granulation methods

Several granulation methods have been used to produce FDDTs. These include wet granulation, dry granulation, melt granulation, spray drying and flash heating.

1.1.3.1.1. Wet granulation

The preparation of formulations for tableting by wet granulation is the oldest method and is the chosen method for drugs that have poor flowability and low compressibility. This method involves wet massing of a blend of active and tableting excipient powders using a binder solution followed by milling, screening and drying to form granules. The granules are milled, sieved and blended with lubricants before compression into tablets (Ishikawa et al., 1999; Lieberman et al., 1990; Sastry et al., 2000).

Wet granulation has been extensively studied as a method for formulating FDDTs. Various formulation and process parameters such as high solubility excipients, osmotic agents, formation of porous granules and tablets have been explored. In addition, the effect of increases in compression force and/or tablet size on FDDT disintegration and hardness have been studied. Based on the granulation technique, three technologies have been patented. These include: OraQuick®, Frosta® and Fast melt®. The patents as well as formulation parameters studied are reviewed below.

1. OraQuick® patented by Grimshaw et al., (2008), KV Pharmaceutical Company; St. Louis, MI, US, applied this method to formulate hyoscyamine sulfate, an antispasmodic medication. The granulation matrix used was microcrystalline cellulose and spray dried mannitol (Mannogem EZ). The resultant granules were blended with spray dried mannitol, microcrystalline cellulose, aspartame, silicon dioxide colloidal, peppermint flavour, crospovidone and magnesium stearate and were compressed into 7mm flat-faced tablets. The authors reported low weight loss during the friability test of

less than 0.17%. The porosity of the tablets was found to be between 21.12 - 23.23%. An excellent disintegration time of below 8 seconds was observed. Hyoscyamine Sulfate ODT, an antispasmodic medication (ETHEX Corporation), is manufactured and marketed by using OraQuick® technology.

2. Frosta® technology was developed by Fu et al., (2005); Jeong et al., (2005). The authors propose that highly plastic granules compressed at low compression force could aid in the formation of porous tablets. The highly plastic granules are formed by wet granulation of three components; a porous and plastic material, mannitol (Mannogem EZ), a water penetration enhancer, porous and non-porous maltodextrin (Maltrin®) and a wet binder i.e. sucrose solution. A high concentration of the sucrose solution helped to achieve the required tensile strength of the tablets at low compression force while maintaining the porous nature of the tablet. The placebo Frosta® tablets are mechanically strong with a friability of <1%. The disintegration time was found to be below 10 seconds. Jeong and Park, 2008 prepared sustained release fast disintegrating tablets of dextromethorphan hydrobromide monohydrate (DM), an antitussive - cough suppressant. The drug was first complexed with the resin (Amberlite® IRP69, polystyrene sulfonate, Na^+ form, crosslinkage of 8%) and was coated with ethylcellulose (EC) and polyvinyl acetate, Kollicoat® SR30D. The coated particles were then granulated, using the Frosta® technology. The resultant tablets showed a short disintegration time between 10 and 30 seconds. The authors report a decrease in tablet porosity with an increase in compression pressure and at a compression pressure of higher than 2.22kN, the tablet was rendered non-porous giving an increased disintegration time of more than 1 minute.

3. Fast melt® was developed by Bonadeo et al., (2000), Elan Pharma, Dublin, Ireland using a wet granulation technique. The resultant granules based on mixtures of polyols, such as mannitol or sorbitol and water-soluble or water dispersible polymers such as polyethylene glycols, or sodium carboxymethyl

cellulose, were blended with an effervescent excipient (sodium bicarbonate and citric acid), the active, magnesium stearate and flavours and were tableted to form large, 16-19mm diameter tablets of 1-2g tablet weight. The authors claimed that the use of only the acid component (citric acid) of the effervescent excipients can lead to fast disintegration of tablets. The disintegration time of the tablets was reported to range from 30 seconds to 3 minutes.

This technology was subsequently adapted to prepare fast dissolving tablets containing 100mg of nimesulide without the addition of the effervescent excipients. The disintegration time of these tablets are reported to be between 30 seconds - 3 minutes (Jain et al., 2007).

Using wet granulation, Bi et al., (1996) prepared rapidly disintegrating flat faced tablets of 8mm diameter. The matrix used comprised of microcrystalline and low substituted hydroxypropyl cellulose and showed low disintegration times below 55 seconds and as low as 25 seconds. It was reported however that the inability of being disintegrated into primary particles resulted in an unpleasant sensation in the patient's mouth.

Okuda et al., (2009) prepared new orally disintegrating tablets using rapidly disintegrating granules of trehalose, mannitol or lactose spray coated with a suspension of corn starch using a fluid bed granulator. As an additional disintegrant, crospovidone, light anhydrous silicic acid, or hydroxypropyl starch was also included in the suspension. Tablets produced using mannitol spray coated with a suspension of corn starch and crospovidone (2.5:1w/w ratio) showed disintegration times of less than 30 seconds.

Fast disintegrating tablets consisting of sustained release multiparticulates of ibuprofen were prepared by wet granulation by Abbaspour et al., (2008). Multiparticulates of ibuprofen were first prepared by using a coating

formulation containing a 4:1 ratio of Eudragit RS 30D and Eudragit RL 30D. The microparticles were blended with granules consisting of microcrystalline cellulose (Avicel® PH 101), cross linked polyvinylpyrrolidone (Kollidon XL) and polyethylene glycol 400 (PEG400) prepared by wet granulation. The blend was compressed at 5kN using flat-faced punches with a diameter of 10mm. The blend consisting of 60%w/w Avicel, 10%w/w cross-linked PVP and 30%w/w PEG 4000 was found to be most suitable for the preparation of fast disintegrating tablets. For the placebo tablets, the hardness was found to be 8.8kg and the disintegration time was 5 seconds. However, inclusion of pellets of ibuprofen caused an increase in the disintegration time of the tablets. At a pellet content of 60 to 80% an increase in DT from 1 to 2 minutes was observed with an increase in hardness from 8.8 to 9.6kg and friability from 2.3 to 5.4%. As the compression force was increased from 5kN, 10kN and 15kN, the authors found an increase in disintegration time of the tablets from 1 minute to 3 and 15 minutes respectively, while the friability was decreased from 2.6% to 0.4% and 0.05%, respectively.

Fast disintegrating tablets consisting of enteric coated microgranules of lansoprazole were prepared by wet granulation technique by Shimizu et al., (2003) using mannitol, citric acid solution, low-substituted hydroxypropyl cellulose (L-HPC-33), microcrystalline cellulose, crospovidone and aspartame. Tablets of 570mg in weight were prepared at three different compression forces of 20, 25, and 30kN using 12 mm punches. As the enteric coated microgranule content increased from 37.5% to 64.3% in a total tablet weight of 420mg to 720mg, a consistent decrease in tensile strength from 51.6 to 12.0N/cm^2 was observed. In addition, a decrease in tablet disintegration time from 49.2 to 9.7 seconds was reported. An increase in tablet compression force from 20 to 25 and 30kN resulted in a corresponding increase in tensile strength from 25.3 to 38.2 and 41.8N/cm^2 and in disintegration time from 30.3 to 33.2 and 46.3 seconds, respectively.

In general, FDTs formulated using wet granulation methods result in tablets with low disintegration time and high tensile strength. The use of hydrophilic actives helped in decreasing the disintegration time of the tablets. Small size tablets (10-12mm) were prepared as favourable FDTs having a DT of less than 30 seconds and friability of less than 1%. An increase in compression force caused a decrease in porosity, increase in hardness and DT.

The greatest disadvantages of wet granulation are the time, energy consumption and considerable material handling equipment involved. The process requires a number of processing steps, is labour-intensive and complex from a validation and control view point (Swarbrick and Boylan, 1991; Yasmeen et al., 2005).

1.1.3.1.2. Dry granulation

Dry granulation in comparison to wet granulation does not require a drying step and hence is energy efficient. The process consists of dry blending of the active with a suitable filler, disintegrant and binder and is subject to compaction followed by milling and screening. The granules formed may be subject to a number of compaction, milling and screening cycles before blending with further disintegrant, glidant and lubricant and compression.

The Flashtab® technology developed by Cousin et al., (1995), Prographarm Group, is based on dry granulation. Tablets containing the active can be incorporated in its original form or as coated microcrystals or granules up to a unit dose of 650mg. Fast dissolution/disintegration is mainly achieved by using disintegrating agents, such as carboxymethylcellulose or insoluble reticulated polyvinylpyrrolidone; and swelling agents, such as carboxymethylcellulose, starch and modified starch. The hydrophilic excipients employed facilitate water entry into the tablet. The tablets are reported to have a disintegration time of less than 1 minute.

A disadvantage of this technology is the high level of disintegrants (upto 50%) which gives a chalky or dry feel when placed in the mouth.

Examples of commercial Flashtab® products are Nurofen Flashtab®, which contains Ibuprofen, a non-steroidal anti-inflammatory drug (Boots Healthcare) and Excedrin Quicktabs® (Flashtab® technology) that contains paracetamol. The composition of acetaminophen Quicktabs® is given below in Table 1.3.

Table 1.3: Composition of Excedrin Quicktabs® prepared using FlashTab® technology (reproduced from Gad, 2008)

Name (Company)	Examples	Ingredients
Flashtab (Prographarm/ Ethypharm)	Excedrin Quicktabs	Acetaminophen (500mg), caffeine (65mg), aminoalkyl methacrylate copolymers, citric acid, colloidal silicon dioxide, crospovidone, distilled acetylated monoglycerides, ethylcellulose, flavors, magnesium stearate, mannitol, methacrylester copolymer, polyvinyl acetate, povidone, propylene glycol, propyl gallate, silica gel, sodium lauryl sulfate, sucralose, talc

Eoga and Valia, 1999 used precompacted calcium carbonate, sorbitol instant, peppermint, magnesium stearate and aspartame mixture to prepare FDDTs. However, the tablets required to be chewed for their rapid disintegration. Yamada et al., (2006) produced rapid disintegrating tablets by dry granulation of powdered cellulose, lactose and low substituted - hydroxy propyl cellulose (L-HPC). The granules obtained were mixed with sucrose fatty acid esters as lubricant and colloidal silicon dioxide (Aerosil®) as a flow enhancer and were compressed into tablets. Addition of the L-HPC to the filler was found to aid the rapid disintegration of the tablets. However, the tablets did not possess the required palatability.

While hydrophilic excipients or disintegrants are required to lower the disintegration times of the tablets, the high level of the disintegrants used causes palatability issues, leading to unpleasant taste. In addition, the dry granulation method has also been reported to form tablets that need chewing in order to melt in the mouth.

1.1.3.1.3. Melt granulation

Abdelbary et al., (2004) demonstrated the formulation of fast disintegrating tablets with sufficient hardness using a melt granulation technique. A hydrophilic waxy binder, PEG-6-stearate that has a melting point of 33 - 37°C and HLB value of 9 was used. The PEG-6-stearate not only acted as a binder to increase tablet mechanical strength, but aided in the disintegration of the tablet due to its low melting point and aqueous solubility. Granules of mannitol and paracetamol, were prepared by melt granulation using PEG-6-stearate as the granulating agent, at a temperature of 40-44°C. The granules were blended with the superdisintegrant, croscarmellose sodium at 8.6%w/w, aspartame and magnesium stearate and tableted. Tablets obtained had disintegration times of greater than 1 minute. A disadvantage of this method is that it is not applicable to heat sensitive actives.

Using a process of heat and shear, Cherukuri et al., (1996) and Myers et al., (1997) designed a new process for the formulation fast disintegrating tablets called Flashdose® technology. Flashdose® technology was used to produce a shearform matrix or floss from the tablet ingredients that consist of the carrier sucrose, a binder sorbitol and a surfactant. During this process, the saccharide is subjected to increased levels of temperature and spun resulting in the conversion of crystalline sugar into its amorphous form. This shearform matrix is then mixed with the API, other tableting excipients and flavours, and compressed under low pressures. This is followed by curing of the tablets under environmental conditions of temperature and humidity levels. During

this curing phase, the tablets increase in tensile strength due to a controlled conversion of the amorphous matrix to a crystalline matrix.

A limitation of the technology is that as the material is subjected to temperature gradient conditions, it may not be applicable to heat sensitive actives.

Misra et al., (1999a); and Misra et al., (1999b), subsequently describe shearform formulations which can be prepared to form single floss (unifloss), or dual floss to have properties of self binding and flowability. The single floss usually consists of sucrose as the carrier with one or two sugar alcohols, xylitol and sorbitol. The dual floss is a combination of a base floss of sucrose and sorbitol and binder floss prepared using sorbitol as carrier and one sugar alcohol, xylitol. Due to the hygroscopic nature of the amorphous sugars, the matrices will absorb moisture, turning into a crystalline matrix, providing compressibility and flowability to the formulation, to allow for ease of tableting.

The FlashDose® matrices have satisfactory mechanical strength and on contact with water readily disperse to release the active. The DT for placebo Flashdose® tablets of diameter 11.1mm was reported to be 18 seconds while the DT of the Nurofen Meltlets® (diameter 15mm) which contains Ibuprofen led to lower mechanical strength of the tablet and slower disintegration of 31 seconds (El-Arini and Clas, 2002). This technology has been applied to the commercially available, Ralivia FlashDose® which contains tramadol HCl, Zolpidem ODT® which contains zolpidem tartrate, and Fluoxetine ODT® which contains the antidepressant fluoxetine (Biovail).

The high temperature gradients used during the formation of shearform matrix limits its application to thermosensitive actives.

1.1.3.1.4. Spray drying

Spray drying is a versatile process which has been utilised for a wide range of applications including microencapsulation, granulation, drying of pharmaceuticals, production of directly compressible excipients and for the preparation of solid dispersion systems (Allen Jr and Wang, 1996; Allen Jr et al., 1998; Allen and Wang, 2001).

As a granulation method, spray drying offers an easily scalable process where an aqueous slurry of the drug, filler, and disintegrants is spray dried to form a porous particulate powder that is further mixed with other tableting excipients including a disintegrant and compressed into tablets. Alternatively, the tablet matrix can be granulated without the active and subsequently blended with the active and other tableting aids and compressed. Advantages of spray dried granulate include good flowability and compressibility of granules and high porosity of the granules which enhances water uptake and disintegration of the tablet.
Mishra et al., (2006) prepared 8mm biconvex tablets by compression using spray dried granules of excipients and the same excipients in their original non-spray dried form. The model drugs used were valdecoxib and metoclopramide. The excipients used were a combination of mannitol and microcrystalline cellulose (MCC) as the filler and one of the following three superdisintegrants at 5%w/w concentration: croscarmellose sodium (Ac-di-sol), sodium starch glycollate or crospovidone (Kollidon CL). Aspartame was used as a sweetener and magnesium stearate as a lubricant. The authors reported improved rheological properties of the spray dried excipient granules (SDE) compared with excipients in their original form. Tablets containing Kollidon CL in SDE base was shown to disintegrate within 20 seconds.

Pharmburst™ technology developed by SPI Pharma utilises a co-processed spray dried excipient for formulating FDTs. Xu et al., (2008) attempted to prepare orally disintegrating tablets (ODTs) by direct compression of co-spray

dried FDT excipients and taste masked microspheres of famotidine prepared using spray drying. The release characteristics and bioavailability of the model drug was not affected by microsphere formation. The compressed tablets disintegrated in the buccal cavity within 32 seconds. The hardness was low, at 20N.

A number of pharmaceutical and tableting excipient suppliers have developed spray dried fillers and co-processed fillers and other excipients using spray drying. These spray dried fillers are supplied for use as a direct compression bases (DCBs) for the formulation of tablets including fast disintegrating tablets. A list of such co-processed DC excipients is given in Table 1.4 below.

Table 1.4 Co-processed DC excipients prepared by various pharmaceutical & tableting excipient suppliers for the development of fast disintegrating tablets

Brand name	Supplier	Composition	Comments
Ludipress®	BASF	lactose monohydrate + Kollidon® 30 + Kollidon® CL	-
MannogemEZ	SPI Pharma	spray dried mannitol	-
Ludiflash®/ Advantol™	BASF	mannitol, crospovidone as a superdisintegrant and polyvinylacetate as a binder	-
F-Melt® Tanaka et al 2007	Fuji Chemical Industry	co-spray-dried powder combining inorganic excipients and disintegrants dispersed in a carbohydrate complex	Fast melting property is linked to the porous structure
Prosolv® ODT	JRS Pharm	co-spray drying microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose and crospovidone	-

1.1.3.2. Tableting based on direct compression

The development of the fast melt tablets using direct compression involves a one-step process, where the API and the tableting excipients are blended and subsequently tableted on a conventional rotary tablet press. Fast disintegrating dissolving tablets (FDDTs) produced by direct compression are based on the single or combined action of disintegrants, water-soluble excipients and effervescent agents. Disintegrants play a major role in the disintegration and dissolution processes. The water taken up by disintegrant particles generates a force inside the tablet and leads to consequent breaking of particle-particle links within the tablets (Massimo et al., 2003). Therefore, the choice of a suitable disintegrant at an optimal amount is critical for fast disintegration and dissolution.

OraSolv® technology based on direct compression was developed for the production of fast disintegrating tablets by Wehling and Schuehle, (1996); Wehling et al., (1993), assigned to CIMA labs (Eden Prairie, MN, US). This technology utilises effervescent excipients in its matrix at 20-25%w/w of the total tablet weight to provide fast disintegration of the tablet. The tablets are compressed under low compression force giving them a low mechanical strength. The combination of effervescent excipients and low mechanical strengths of the FDDTs require specialised packaging such as Paksolv®, (Amborn and Tiger, 2001) a dome-shaped blister which is designed to minimise tablet movement within the blister pack as well as protecting the tablet from moisture and light allowing safe transport of the intact tablets to the patient. The OraSolv® technology can include the drug as microparticulates, and is reported to accommodate high dose of actives of up to 750mg/ unit. The disintegration time is claimed to be between 30 seconds - 7 minutes.

Examples of commercially available fast disintegrating dissolving tablets prepared using this technology include Tempra Quicklets® and Tempra

FirsTabs® which contain paracetamol, Remeron SolTab® (diameter 9.7mm, DT 56.6 seconds) which contains mirtazepine an antidepressant and Triaminic Softchews® which contains chlorpheniramine and pseudoephedrine (Allen et al., 2005; Klancke, 2003; McLaughlin et al., 2009). The composition of Remeron SolTab® is outlined in Table 1.5.

Table 1.5: Composition of Remeron Soltab® prepared using the OraSolv® technology (reproduced from Gad, 2008)

Name (Company)	Examples	Ingredients
Orasolv® (CIMA Labs Inc.)	Remeron Soltab	Mirtazepine (15, 30, or 45mg), aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polymethacrylate, povidone, sodium bicarbonate, starch, sucrose, orange flavor

CIMA Labs developed a second generation of fast disintegrating tablet technology, the DuraSolv® technology (Khankari et al., 2001) which contains taste masked microparticles of active of up to 500mg dose per unit. This new formulation approach produces tablets of higher mechanical strength while retaining the primary benefits of fast disintegration in the mouth. It therefore allows the use of conventional blister packaging.

The key ingredients of the DuraSolv® technology are non-direct compression sugar, a direct compression sugar, an effervescent agent, a wicking agent and a lubricant. The resultant tablets had friability values of less than 2%. The patent claims disintegration/dissolution time in the patient's mouth of 45-90 seconds. The *in vitro* disintegration time of the placebo DuraSolv® tablets is reported to be 36 seconds (El-Arini and Clas, 2002).

Examples of fast disintegrating dissolving tablets prepared by the DuraSolv® technology include: Zomig-ZMT® containing zolmitriptan; (AstraZeneca), Alavert® which contains loratadine; (Wyeth Consumer Healthcare) and Kemstro™ which contains baclofen; (Schwarz Pharma).

Effervescent formulations are generally sensitive to moisture, hence requiring production under a humidity control environment. In addition, packaging of the final dosage form requires moisture impermeable blisters. To alleviate this issue, Jacob et al., (2009), formulated novel effervescent based fast disintegrating 10mm flat faced tablets. Both of the effervescent salts involved in the effervescent reaction were coated to provide a physical barrier to the reaction between acid and basic effervescent component and also to act as a protective coating from the atmospheric conditions.

Citric acid/tartaric acid/sodium hydrogen citrate was granulated with polyethylene glycol 1000 (PEG) using absolute ethanol and then granulated with microcrystalline cellulose whereas sodium bicarbonate/sodium glycine carbonate was blended with mannitol. The inherent hygroscopic nature of PEG could decrease the affinity for moisture of effervescent mixtures and can provide a stabilising effect. At body temperature, PEG melts allowing the reaction between the acid source and base. The FDDTs were compressed at low compression force and contain additional disintegrants such as 7.1% of croscarmellose sodium and 7.1% of corn starch to give tablets of porosity ranging 14.95 to 22.13%, and corresponding DT of 42 to 32 seconds, and friability (% weight loss) of 1.94 to 0.69%, respectively.

The Ziplets® technology developed by Dobetti, 2003 (Eurand, Italy) is based on direct compression and is applicable for the formulation of fast disintegrating tablets containing actives or coated microparticles. The fast disintegrating dissolving tablets are obtained by direct compression at low compression force using a water insoluble inorganic excipient e.g. calcium phosphate, one or more superdisintegrants such as crospovidone and cross-

linked carboxymethylcellulose at greater than 10%w/w of the formulation or alternatively a water-soluble excipient. Addition of insoluble compounds is perceived to increase the efficiency of the superdisintegrant by not competing for the disintegration medium with the superdisintegrants. The tablets were reported to possess optimal disintegration time and excellent physical resistance with friability values of less than 2%, allowing the use of conventional blister packs for packaging. As the dose of active was increased from 20-450mg, and tablet weight from 228 to 850mg, a corresponding increase in hardness (18 to 49N), friability (0.7 to 1%) and *in-vivo* DT (15 to 40 seconds) was observed (Dobetti, 2000). Commercially available tablets based on this technology include Cibalginadue FAST which contains Ibuprofen, (NSAID, Novartis Consumer Health) (Allen et al., 2005; Klancke, 2003).

AdvaTab™ technology is a second FDDT technology based on direct compression developed by Hayakawa et al., (2002) (Tokyo, Japan) and assigned to Eurand America. It uses an external lubrication system instead of an internal lubrication system that is usually carried out during the manufacture of conventional tablets. Since the system utilises 10-30 times less hydrophobic lubricant than conventional tablets, it therefore produces tablets that are 30-40% stronger than conventional tablets. The tablets are also less friable and can be packaged in bottles or blisters. Current marketed products based on AdvaTab® technology are Lamictal® ODT™ (lamotrigine) Orally Disintegrating Tablets, co-developed with GlaxoSmithKline and Paracetamol ODT Orodispersible Tablets (Allen et al., 2005; Klancke, 2003).

Modifications of the direct compression technology have been studied to confer enhanced mechanical strength to the FDDTs. Shu et al., (2002) used co-ground mixtures of mannitol and crospovidone and non-ground mixtures of mannitol, crospovidone and magnesium stearate to formulate fast disintegrating tablets by direct compression. They found that addition of the co-ground mixture of mannitol and crospovidone to the unground mannitol, crospovidone (Polyplasdone® XL) and magnesium stearate helped in the

formation of rigid tablets. This was due to the increase in contact between component particles resulting in increased hardness of the tablets.

Khan et al., (2007) explored the use of various superdisintegrants for the formulation of 8mm flat faced fast disintegrating tablets containing taste masked ondansetron HCl, prepared by direct compression. A number of superdisintegrants were used, crospovidone, croscarmellose sodium (CCS), and sodium starch glycollate (SSG). The author observed that when microcrystalline cellulose (MCC) and spray-dried mannitol (SD-M) were used in the ratio 1:1, the disintegration time of the tablets containing either CCS or SSG was concentration dependent. At increasing disintegrant concentrations of 8 - 12%w/w, DT for CCS decreased from 31 to 18 seconds while for SSG the DT decreased from 42 to 32 seconds. Crospovidone showed the lowest DT in the range of 7-11 seconds, when used in the concentration range of 5-12%.

Battu et al., (2007) similarly investigated the use of the superdisintegrant crospovidone, CCS and SSG using a combination of mannitol to MCC in the ratio 3:1. They report the fastest disintegration for crospovidone similar to Khan et al., (2007). Further, the disintegration time they report for SSG was shorter at 38-28 seconds than for CCS at 71-39 seconds.

Yang et al., (2004) investigated a novel amorphous disintegrant, polyacrylic superporous hydrogel (SPH), for the formulation of ketoprofen fast disintegrating tablets. Due to its porous nature, the disintegration mechanism of SPH was hypothesised to be by wicking action of the dissolution medium into the tablet and it is reported to swell by 80-times in distilled water. Flat faced 12.5mm tablets of 500mg were prepared using ketoprofen as a model drug and dextrates and mannitol as water-soluble filler. Citric acid and aspartame were used as flavours to mask the unpleasant taste of ketoprofen. The resultant tablets possessed an acceptable tensile strength with disintegration times of less than 20 seconds. At high compression force,

tablets with a lower porosity were produced and a corresponding increase in the tensile strength and DT of the tablets was observed.

Fini et al., (2008) formulated mannitol-based FDDTs at low compression force. The disintegrant used was crospovidone (Kollidon CL) or sodium starch glycollate (Explotab, SSG). When taste masked granules of ibuprofen were included in the formulation, a DT of greater than 1 minute was observed for SSG, while for Kollidon CL it was 32 seconds.

Rapidly disintegrating tablets (8mm) were formed using taste masked granules of pirenzepine HCl or oxybutynin HCl prepared by the extrusion method using aminoalkyl methacrylate copolymers (Eudragit E100) and ethanol. Rapidly disintegrating tablets were prepared by direct compression from a mixture containing crystalline cellulose (Avicel PH-102) and L-HPC in the ratio 8:2 with taste masked granules, and 1%w/w of magnesium stearate. The mechanical strength of the tablets varied depending on the type of drug used (oxybutynin tablet, 3.5kg; pirenzepine tablet, 2.2kg). The resultant tablets disintegrated within 20 seconds. However, L-HPC used as disintegrant at a high concentration of 10-17%w/w of the formulation, is regarded to impart a rough texture to the formulation (Ishikawa et al., 1999).

Rawas-Qalaji et al., (2006) evaluated the influence of an increase in the water-soluble hormone, adrenaline (epinephrine), loading and increase in compression force on the characteristics of fast disintegrating tablets prepared by direct compression. They used epinephrine at 0, 5, 10 and 20mg per 150mg tablet. The tablets were prepared using microcrystalline cellulose (Avicel® PH-301), low-substituted hydroxypropyl cellulose (LH11) (9%w/w) and magnesium stearate (2%w/w) at various compression force ranging 21.5 - 24kN. With an increase in drug load from 0 to 20mg, a corresponding decrease in hardness from 12 to 2kg and DT from 37.2 to 5.6 seconds was observed. An increase in compression force from 21.5 to 24kN led to an

increase in the hardness of tablets from 1.9 to 12kg and DT from 2.2 to 37.2 seconds.

From the above review of direct compression as a technology for the formulation of fast disintegrating tablets, it was observed that the type of disintegrants used could confer different DT depending on their disintegration mechanism. Crospovidone, which acts by a wicking mechanism, showed the lowest DT in most cases. Compression force (CF) is known to affect tablet hardness and DT. An increase in CF leads to a decrease in porosity and an increase in hardness and DT of tablets. Therefore a lower CF has been utilised by many researchers and proprietary technologies, for formulating tablets with low mechanical strength to give fast disintegration.

The type of filler, inclusion of the active and physicochemical properties of active can also have significant effects on the characteristics of the final FDTs.

1.1.3.2.1. Compaction followed by subsequent treatments

The key properties for fast disintegrating tablets are high porosity compacts for effective fast disintegration and good mechanical strength for safe handling. In order to enhance these properties a number of strategies have been examined post compaction of the tablets. These include post treatments like sublimation, humidity treatment and are described below.

1.1.3.3.1.1. Sublimation

Sublimation is the transition of a substance from the solid phase to the gas phase without undergoing intermediate liquification. Therefore, like lyophilisation process, it is effective in creating porous tablets. To allow the formation of high porosity tablets, a subliming material such as camphor, thymol or menthol is included in the tablet matrix which when subject to sublimation, volatilises leaving a porous matrix and hence low DT.

Koizumi et al., (1997) formulated FDDTs with camphor and mannitol and subjected these to sublimation (Figure 1.3). Highly porous tablets were formed due to the formation of many pores where camphor particles previously existed. The compressed tablets showed high porosity at approximately 30% and rapidly disintegrated/dissolved within 15 seconds in saliva.

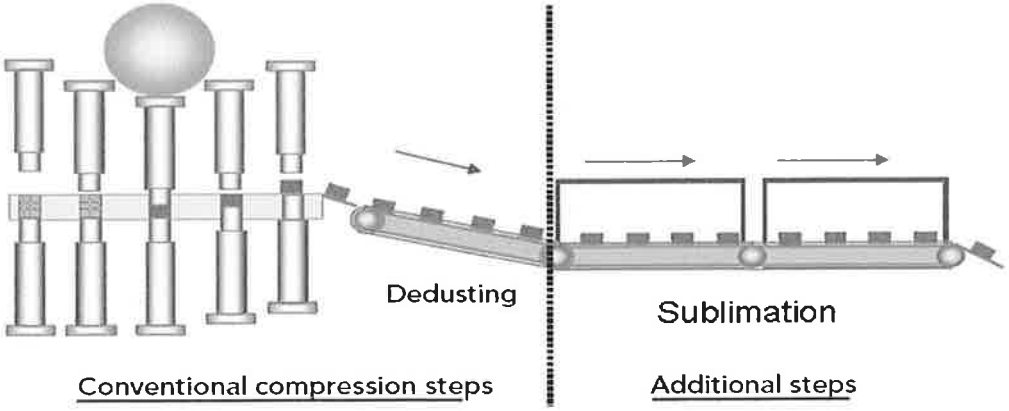


Figure 1.3: Compaction followed by subsequent treatment, sublimation (adapted from Fu et al (2004))

Gohel et al (2004) prepared fast disintegrating tablets of nimesulide by a sublimation process. Granules containing nimesulide, crospovidone, lactose or microcrystalline cellulose or dicalcium phosphate were prepared by a wet granulation technique. Subliming agents such as menthol, camphor or thymol were added during the granulation process. The subliming agents were sublimed from the dried granules by exposure to vacuum for 5-10 hours. The porous granules were then compressed. Alternatively, tablets were first prepared and later exposed to vacuum. The tablets were evaluated for friability and DT. Sublimation of camphor from the compressed tablets resulted in lower DT in comparison to tablets formulated from sublimed granules. The tablets prepared showed low friability at less than 1%.

The manufacturing methods of these tablets are intensive, laborious and time consuming.

1.1.3.3.1.2. Phase transition method (amorphous to crystalline)

The phase transition method is based on the basic concept that an amorphous solid is a solid with a disordered structure. The amorphous substance has no long-range order of the positions of the atoms, however when converted into its crystalline form, it tends to have a highly ordered arrangement of atoms in which there is long-range atomic order and therefore stronger bonds than its amorphous counterparts. This concept was exploited for improving the mechanical strength of tablets post compression. A sugar based material is converted into its amorphous form using techniques such as freeze drying or granulation. The granules are then compressed into tablets and subjected to various treatments during which conversion of the amorphous sugar into its crystalline form results in the formation of strong interparticulate bonds, and hence tablets with high mechanical strength.

Mizumoto et al., (1996); Mizumoto et al., (2003); and Mizumoto et al., (2005) prepared granules using a low compressibility saccharide such as lactose, sorbitol, trehalose, lactilol, which has the potential of being converted into an amorphous form. The granules were subsequently tableted using a low compression force. The tablets were subjected to a conditioning process (for 24 hours at 25°C 70% R.H. followed by a further period of 3 hours at 30°C and 40% R.H.) to enable conversion of the amorphous phase into its crystalline form in order to strengthen adhesion between the particles to achieve sufficient hardness. This technique forms the basis of the WOWTAB® technology (Yamanouchi-Shaklee Pharmaceutical (Tokyo, Japan).

Liu et al., (2002) (Yamanouchi Pharmaceutical Co., Ltd. (Tokyo, Japan)) also reported a two step treatment process in which the tablets were first subject to a humidification process at 25°C and 85% R.H. for 30 minutes, followed by

drying at 40°C and 30% R.H. for 30 minutes. The final tablet product was found to be strong enough to be packaged or stored in bulk. The friability of the resultant tablets was reported to be below 1%, and tablets disintegrated within 10-15 seconds.

Examples of currently available fast disintegrating tablets based on this technology include Benadryl® Fastmelt® (diameter 11.2mm, DT 15.7 seconds) which contains diphenhydramine citrate (Pfizer), Nasea OD which contains ramosetoron HCl (Yamanouchi) (Fu et al., 2004; McLaughlin et al., 2009). The ingredients contained in Benadryl® Fastmelt® are outlined in Table 1.6.

Table 1.6: Composition of Benadryl® Fastmelt® by using WOWTAB® technology (reproduced from Gad, 2008)

Name (Company)	Examples	Ingredients
WOWTAB (Yamnouchi Pharma technologies Inc.)	Benadryl Allergy & Sinus Fastmelt	Diphenhydramine citrate *(19 mg)* pseudoephedrine HCl *(30 mg)* aspartame; citric acid, D & C red no. 7 calcium lake, ethylcellulose, flavor, lactilol, magnesium stearate, mannitol, and stearic acid

Bi et al., (2000) used the basics of the WOWTAB® technology to prepare fast disintegrating tablets. They used alpha lactose monohydrate powder and wet granulated it to render it amorphous. Lactose was kneaded with water and the wet powder mass was then extruded through the sieve. The wet granules were then compressed into tablets under low compression force. The wet tablets were dried in a circulating oven at 60°C after which the tablets were stored in a dessicator for 12 hours at room temperature. An increase in tensile strength of the tablets after storage was identified and this was related to the solid bridges formed between the lactose particles resulting from the re-

crystallization of lactose. The tablets had high porosity of 26-28% and low disintegration time of 15 seconds. Lactose of smaller particle size (13.18μm) is reported to be preferable as it allows for large surface area and greater points of contact between the particles, and thus giving better tensile strength to the tablets.

Sugimoto et al., (2001) developed a phase transition method to prepare tablets with low disintegration time and high mechanical strength. He formulated 10mm flat faced tablets at low compression force from a mixture containing mannitol powder and freeze dried amorphous sucrose. Subsequently, he stored these tablets at 25°C and 34% R.H. for five days to allow conversion of amorphous sugar into its crystalline form (Figure 1.4). This results in the formation of strong interparticulate bonds, hence giving an increase in the tensile strength of the tablets. This method is called the crystalline phase transition method. External lubrication was used in this instance, whereby punches and dies were lubricated using a cotton swab prior to compression.

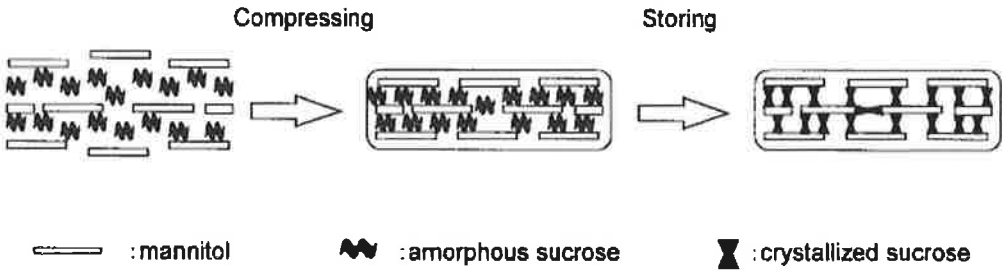


Figure 1.4: Schematic illustration of the internal structure of the mannitol tablet showing the crystallization of freeze-dried sucrose (reproduced from Sugimoto et al 2001).

The use of this technique for an industrial scale production of rapid disintegrating tablets with sufficient tensile strength was investigated by Sugimoto et al., (2006a). He prepared granules of mannitol using sucrose as a binder in a fluidized bed dryer. These granules were then compressed under low compression force and stored at 25°C and 51% R.H. for 2days in a

dessicator. During storage, the amorphous sucrose formed during the granulation step undergoes crystalline transition resulting in the formation of new internal solid bridges, and hence sugar tablets with required tensile strength. However, this method was reported to be suitable for the formulation of fast disintegrating tablets of highly water-soluble actives only (Sugimoto et al., 2006b).

Rapid disintegrating tablets prepared by phase transition of sugar alcohols were also studied by Kuno et al., (2005). Tablets were formulated from granules prepared using a high melting point sugar alcohol, erythritol; 121°C, and a low melting point sugar alcohol, xylitol; melting point 92°C, in a fluidized bed granulator. The tablets obtained were subsequently heated at 93°C for 15 minutes by placing in a drying oven and then were allowed to cool in a petri dish at 25°C/65% R.H. for 4 hours. The hardness of tablets increased after the 4 hours storage period and this was hypothesised to be due to the formation of inter-particle bonds or in an increase in bonding surface area induced by the softening of xylitol into amorphous form and its subsequent solidification on cooling into its crystalline form. The disintegration time of the tablets was found to be below 30 seconds, due to the porous nature of the tablet (Figure 1.5).

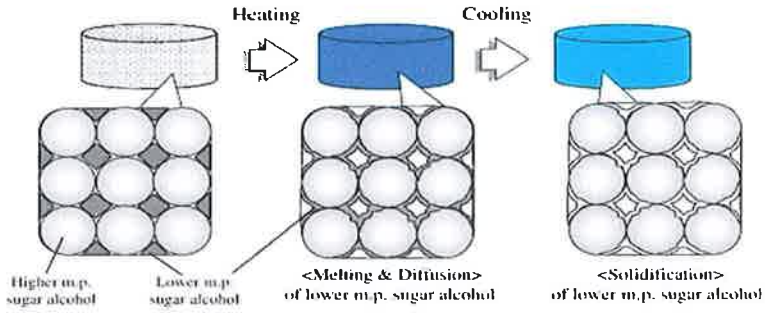


Figure 1.5: Schematic description of the phase transition preparation process for rapidly disintegrating tablets (adapted from Kuno et al 2005).

A brief summary of the various FDDT technologies reviewed together with their advantages and disadvantage are given in Tables 1.7a & b.

Table 1.7a: A brief summary of FDDT technologies available and its related advantages and disadvantages

Technology	Advantages	Disadvantages
Lyophilization Zydis® Quicksolv® Lyoc® Nanocrystal technology™	High porosity tablets Immediate dissolution (2-10 seconds)	Poor physical resistance requires specialized packing High production cost Sensitive to humidity Low dose (<60mg) of water-soluble drugs
Moulding	Very rapid dissolution (5-15 seconds) High dose	Weak mechanical strength High production cost stability limitations
Wet granulation OraQuick® Frosta® Fast melt®	Applicable to poorly compressible and poorly flowable actives	Multiple processing steps, labour and time intensive Not applicable to moisture and heat sensitive materials
Melt granulation Flashtab®	satisfactory mechanical strength, fast dispersibility of tablets, inclusion of high active doses	Not applicable to heat sensitive actives
Dry granulation Flashdose®	High dose of active upto 650mg	high levels of disintegrants Poor palatability; chalky and dry feel

Table 1.7b: A brief summary of DC technologies and modifications used to formulate FDDTs with related advantages and disadvantages

Technology	Advantages	Disadvantages
Direct compression	cost effective, one step process, applicable to wide range of actives	
Ziplets® (low CF)	Use of standard equipment	Significant effects of tablet size, dose on hardness and DT. not applicable to water-soluble compounds
With effervescent formula	Use of standard equipment	Disintegration limited by size of tablets
OraSolv®* DuraSolv® AdvaTab™	High dose (>600mg) (except OraSolv®) Pleasant effervescent mouth feel	requires humidity control, need impermeable blister, higher friability, external lubrication system adds to the cost of the process for AdvaTab™
DC + post-treatment		
(1) Sublimation	Good physical resistance	Labour and time intensive, Harmful residual adjuvants, Not applicable to volatile and heat sensitive drugs
(2)Phase transition WOWTAB®	Good physical resistance Pleasant mouth feel Independent of active solubility High dose (500mg)	Additional equipments for humidification and drying, Complex and high cost process, Limitations in stability, Not suitable for moisture sensitive compounds

1.2. Microencapsulation

Microencapsulation of therapeutic agents is a process in which very thin coatings of inert natural or synthetic polymeric materials are deposited around the microsized particles of solids or around droplets to form microparticles in size range of less than 500μm to 2mm (Grattard et al., 2002). Microparticles can be categorized into microcapsules, where the drug is coated by the polymer (Figure 1.6a) and microspheres, where the drug is distributed within the polymer matrix (Figure 1.6b) (KristmundsdÛttir, 1996).

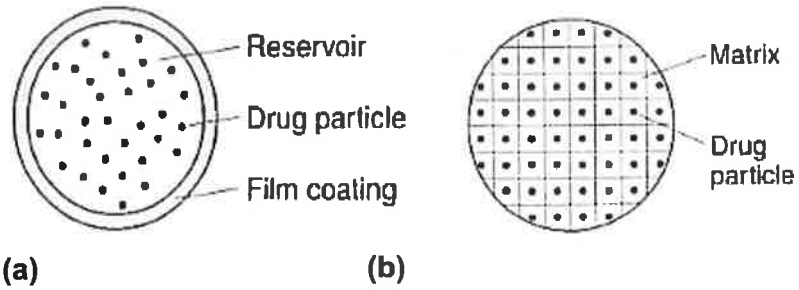


Figure 1.6: Diagrammatic representation of (a) microcapsules and (b) microspheres

Microencapsulation has been advantageously used in many industries including pharmaceutical, food, cosmetics etc. The objectives of microencapsulation in the pharmaceutical industry are to (1) mask the unpleasant taste or odour of the active to make administration easier, contributing in patient compliance (Al-Omran et al., 2002; Zgoulli et al., 1999), (2) to obtain a controlled release form of the active (KristmundsdÛttir, 1996), (3) enteric coating for protection of the active from the stomach environment (Beyger and Nairn, 2006; Lin and Kao, 1991) or (4) film coating to produce stable products i.e. to protect the active against oxidation (Assimopoulou and Papageorgiou, 2004) and spoilage/degradation (Uddin et al., 2001), depending on the physiological, physicochemical, organoleptic and

pharmacological properties of the pharmaceutical agents, and intended use of their products.

Besides having good organoleptic properties, microencapsulation results in a product which has good flowability, compressibility and stability characteristics, making them suitable for further processing. Therefore, these have been formulated into various appropriate oral dosage forms such as tablets (Desai, 2007; Lin and Kao, 1991), hard gelatin capsules (Hosny et al., 1998) or sachets for their further commercialisation. Microparticles are also used for other routes of administration such as pulmonary and parenteral drug delivery and are processed into alternative dose forms suitable for these routes (Sana et al 2004).

As they are multiple units, microparticulates offer several advantages when compared to single unit dosage forms such as coated tablets or capsules. The multiparticulates spread uniformly throughout the gastrointestinal tract, resulting in less variable bioavailability and a reduced risk of local irritation. Various drug release profiles can be obtained by mixing microparticles with different release characteristics. They can also be used to separate incompatible drugs within the final dosage form (Dashevsky et al., 2004). Micro and nanoparticles have also been advantageous for targeted release/site specific release of the API to give increased therapeutic efficacy and reduced side effects (Avgoustakis, 2004).

1.2.1. Microencapsulation Techniques

Over the years, a range of microencapsulation techniques from coacervation, solvent evaporation to coating of nonpareil sugar seeds and spray drying have been developed and utilised. The choice of one particular method is determined to a large extent by the physicochemical and pharmacological properties of drugs, solubility characteristics of the carrier material and intended use of their products (Deasy, 1984; Palomo et al., 1996). Some of the microencapsulation techniques are briefly described below,

1.2.1.1. Air suspension technique

The air suspension technique, invented by Prof Dale E. Wurster, is a process used to coat solid particulate core material with a polymer coating. The drug core particles are suspended in an upward moving air stream and the polymer coat is sprayed onto the cores. The polymer coat spreads onto the surface of the particles and is dried as it is fluidised in the hot air stream (Lieberman et al., 1990). Fluidized bed coating is a widely used technique in the pharmaceutical industry for the microencapsulation of drug particles and coating of pellets for controlled release and film coating applications.

Dashevsky et al., (2004) described the use of fluid bed coating to prepare ethylcellulose coated propranolol HCl granules. Approximately 50% of propranolol HCl was released after 8 hours from the granules. Silva et al., (2006) used a fluidized bed system to prepare enteric coated granules of diclofenac sodium using Eudragit L-30D-55 as the polymer. They showed that approximately 90% of the drug was released from the granules at pH 6.8 in 10 minutes.

Fluidized bed drying was applied for the preparation of microparticles for incorporation into the formulation of fast disintegrating tablets. Alkire et al., (1997) describe the formulation of coated chlorpheniramine maleate (CM) particles using air suspension coating for incorporation into OraSolv® or DuraSolv® FDDT matrices. The CM was first granulated with mannitol and then coated with ethylcellulose using fluidized bed spray coating. The mean particle size of the coated material was 307μm. The dissolution studies carried out on the coated chlorpheniramine maleate granules showed 98.2% dissolution in 10 minutes. Evaluation of the taste of FDDTs prepared using the coated granules concluded that there was no detectable drug aftertaste.

Shimizu et al., (2003) prepared fast disintegrating tablets (FDTs) of lansoprazole consisting of enteric coated microgranules prepared by a wet granulation technique in a fluid bed coater/granulator. The percentage of

lansoprazole dissolved in the 0.1NHCl, pH1.2 was 2.5% after 1 hour, indicative of relatively good enteric coating properties.

1.2.1.2. Coacervation - Phase separation

Microencapsulation by coacervation-phase separation consists of depositing a coating material onto the core material by a process of precipitation of the polymer using a precipitation agent such as a non-solvent for the polymer, pH change or a reduction in temperature. The drug is usually dispersed in the polymer solution or dissolved in an immiscible solvent and emulsified into the polymer solution. On coacervation, the polymer precipitates onto the droplets or drug particles to produce microparticles (Singh and Robinson, 1988).

This technique has been used to prepare controlled release formulations of the poorly soluble drug diclofenac sodium (DFS) using ethylcellulose (EC) as a polymer by Sajeev et al., (2002). The prepared microcapsules were free flowing and spherical in shape, with the particle size varying from 49.94 - 52.72µm. More than 60% of the drug was released after 20 minutes. The drug release was sustained up to 90 minutes at a DFS:EC ratio of 1:3.

Al-Omran et al., (2002) used ethylcellulose to mask the unpleasant taste of diclofenac sodium by forming its microcapsules using a simple organic phase separation process. The microcapsules showed good palatability for inclusion into FDDT formulations.

Sustained release microparticles have been prepared by coacervation - phase separation for inclusion into FDDTs using the DuraSolv® or OraSolv® technologies, CIMA Labs and Eurand's Advatab® ODT technology (Bettman et al., 1997; Harmon, 2006).

1.2.1.3. Pan coating

Pan coating is used for the encapsulation of solid particles greater than 600μm in size. Medicaments are coated onto various spherical substrates such as nonpareil seeds, which are then coated with protective layers of various polymers. The coating is applied as a solution or an atomized spray to the desired core material in the coating pan. The coating solvent is dried in a flow of warm air (Lieberman et al., 1990).

Pan coating as a microencapsulation technique was demonstrated by Hosny et al., (1994) for the preparation of controlled release beads of propranolol HCl using Eudragit RS100 and enteric coated beads of poorly water-soluble diclofenac sodium using Eudragit L100 (Hosny et al., 1998).

The beads were characterised for their particle size distribution, drug loading efficiency and their dissolution behaviour. Propanolol HCl beads were in the particle size range of 800-1700μm. The actual drug content, calculated as opposed to the theoretical drug content were 77.6% and 74.2% for the beads having a particle size range 1700 - 1250μm and 1250 - 800μm respectively. A burst release of approximately 50% propanol HCl was observed after 30 minutes. Subsequent drug release was sustained for up to 3 hours.

Diclofenac sodium enteric-coated beads showed a narrow particle size distribution in which 83% of the beads were in the range of 1-2 mm. The drug loading was 92%. The beads released about 8% of the drug during 2 hours of dissolution in 0.1 N HCl while in phosphate buffer (pH 6.8) the beads released their drug content in 1 hour (Hosny et al., 1998).

1.2.1.4. Solvent evaporation

The solvent evaporation technique is a commonly utilised method in the pharmaceutical industry. In this process, a core material to be

microencapsulated is dissolved or dispersed in the volatile coating polymer solution. Microspheres of appropriate size can be prepared by the addition of the core-coating material mixture into the immiscible liquid external vehicle phase under constant agitation. The characteristics of the microparticles can be altered by monitoring the rate of solvent evaporation, by subjecting it to heating (Lieberman et al., 1990).

A solvent evaporation technique has been used by Remuñán-López et al., (1998) and Palomo et al., (1996), for the preparation of controlled release formulations of poorly soluble drug diclofenac sodium with ethylcellulose as a polymer. Controlled release microparticles of diclofenac sodium were prepared by Remuñán-López et al., (1998) using a double emulsion solvent evaporation technique using hydrophilic chitosan microcores entrapped in a hydrophobic cellulosic polymer, ethylcellulose. The encapsulation efficiency of the resultant particles was found to be more than 90%. The diclofenac sodium release from the microparticles showed approximately 55% of the drug was released after 2 hours in phosphate buffer pH 7.4.

Palomo et al., (1996) formulated microcapsules of diclofenac sodium by solvent evaporation, using ethylcellulose as the polymer to give a sustained release profile of the drug over 8 hours.

Solvent evaporation was also used to enhance the solubility of the poorly water-soluble drug, simvastatin. Patel and Patel, 2008 prepared amorphous solid dispersion of simvastatin with polyethylene glycol (PEG) (crystalline) and Kollidon 30 (PVP) (amorphous) by a solvent evaporation technique and used ethanol as a solvent. The drug was present in amorphous form at high concentration of both polymers. The solubility of simvastatin improved from 8.79% for pure simvastatin to 58.2% and 74.5% for solid dispersions of simvastatin in PEG and PVP respectively.

1.2.1.5. Spray drying & Spray congealing / Spray chilling

1. Spray drying

The spray drying technique is an important and widely applied technique in the pharmaceutical and biochemical fields (Esposito et al., 2000). Spray drying has also been used to prepare other common commercial products including powdered milk, instant coffee, instant foods, and synthetic detergent, in powdered form (Kond, 1979).

To accomplish encapsulation by spray drying technique, a polymer solution containing an active ingredient is atomized as fine droplets using compressed air or nitrogen. The solvent is dried off using heated medium of hot air or nitrogen in a spray dryer, to form globular droplets or microparticles (Figure 1.7). The formed microparticles are separated in the cyclone separator and collected in the collecting vessel (Esposito et al., 2000).

In comparison to other microencapsulation techniques, spray drying is a feasible technique for a wide range of formulations, drugs and polymers, allowing the encapsulation of water-soluble and water insoluble drugs with either hydrophilic or hydrophobic polymers. Microparticles can be formed using, homogeneous one-phase aqueous solutions (Wan et al., 1991) or organic solutions (Ambike et al., 2005) or hydroalcoholic solutions (Esposito et al., 2000) as well as heterogeneous two-phase systems i.e. dispersions (Rattes and Oliveira, 2007) suspensions (Mizumoto et al., 2008) or emulsions (Giunchedi et al., 2000) of core material and film forming or coating material.

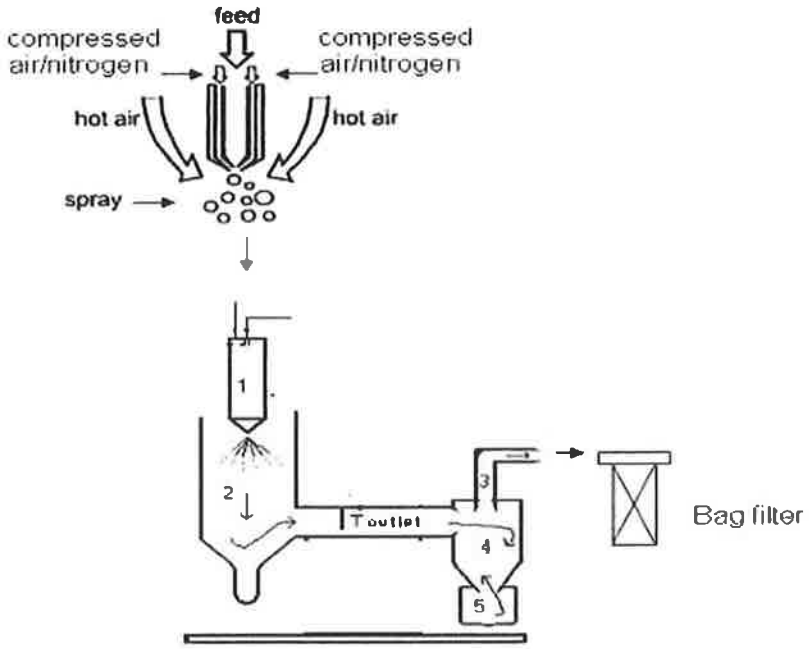


Figure 1.7: The two-fluid nozzle (1) disperses the liquid into fine droplets, which are dried in the drying chamber (2) forming particles, which are then carried to the cyclone separator (4) and eventually carried to the product collecting vessel (5) or exhausted to the bag filter through tubing 3

Polymers used in the microencapsulation of drugs range from film coating, for taste masking, pH sensitive polymers and sustained release (SR) polymers including biodegradable and non-biodegradable polymers. Spray drying as a microencapsulation technique was applied for hydrophilic polymers such as hydroxyl propyl cellulose (Wan et al., 1991), Chitosan (He et al., 1999) and hydrophobic polymers such as Ethylcellulose (Zhang et al., 2000) and Eudragit RS (Esposito et al., 2000) and polymer, PLGA/PEG (Avgoustakis, 2004).

The effect of spray drying process parameters on the characteristics of microparticles formed have been studied and reported. The characteristics of

the particles formed are dependent on spray drying parameters, the type of drug and polymer utilised.

Wan et al., (1991) prepared theophylline coated particles by spray drying with aqueous solutions containing hydroxypropylethylcellulose. The influence of inlet drying temperature, drying air flow rate (air aspirator rate (AAR)), feed spray rate (feed flow rate (FFR)) and atomizing pressure (spray flow rate (SFR)) on microparticles formed was studied. The authors reported that an increase in inlet temperature enhanced the flow properties of the spray dried particles and produced coated particles with a slower drug dissolution rate, probably due to better drying and film formation. Particles produced at a faster drying air flow rate were found to have better flowability. High feed spray rates resulted in ineffective atomization, producing badly formed spray-dried products. Atomizing pressure affected only the particle size of the product formed. The smaller particles had a higher dissolution $T_{50\%}$ and were more cohesive.

He et al., (1999) prepared drug loaded chitosan microspheres by dissolving the model drugs, cimetidine, famotidine or nizatidine in the chitosan aqueous dil. acetic acid solution prior to spray drying. He observed that an increase in feed flow rate was accompanied by an increase in the size of microspheres. An increase in particle size was also observed with a decrease in spray flow rate.

Prinn et al., (2002) examined the effects of formulation and process variables on particle size and other characteristics of a spray dried model protein bovine serum albumin prepared by spray drying aqueous solutions. It was found that a decrease in protein concentration and an increase in atomizing nitrogen pressure (SFR) caused a decrease in particle size.

Esposito et al., (2000) evaluated the influence of operating parameters on the characteristics of Eudragit® microparticles prepared by a spray-drying

technique using a hydroalcoholic solvent. He observed that a decrease in feed flow rates was accompanied with better morphology, decrease in mean particle dimensions, more uniform particle size distribution and high product recovery. A decrease in flow rate of compressed nebulizing air (SFR) was accompanied by some variation in particle dimensions and a decrease in product recovery, without any change in morphology. The authors also reported that an increase in air drying temperature (T_{inlet}) led to a reduction in microparticle dimensions and microparticle recovery whereas microparticle morphology was not influenced by temperature variation.

Rattes and Oliveira, 2007 evaluated the effect of spray drying conditions on the formation and properties of controlled release sodium diclofenac microparticles prepared by spray drying. Aqueous dispersions of ethylcellulose (Surelease) and Eudragit RS30D were evaluated as controlled release polymers. Lower levels of product moisture contents were observed at higher drying temperatures. An increase in the mean particle diameter was found to be directly proportional to the feed flow rate (FFR). A summary of the findings from the studies reported above is compiled in Table 1.8 below.

Table 1.8: Summary of the influence of spray drying process parameters on the characteristics of the products as observed by 5 authors

Spray drying parameters	Particle size	PSD*	Morph-ology	Flow property	Drug release	Product recovery
↑Tinlet	↓[4]	-	NIL[4]	↑ [1,5]	Slow[1]	↓[4]
↑Feed flow rate	↑[2,4,5]	↓[4]	↓[1,4]	-	-	↓[4]
↑Spray flow rate	↓[1,2,3 (4)]	-	NIL[4]	-	-	↑[4]
↑ Air aspiration rate	↑[4]	-	↓[4]	↑[1]	-	-

* particle size distribution (width/span), [(4)] some variation [1] Lucy et al (1991), [2] He et al (1999) [3] Prinn et al (2002) [4] Esposito et al (2000) [5] Rattes et al (2007)

Spray drying has been successfully used by authors to formulate controlled release preparations of the poorly water-soluble drug diclofenac sodium (Desai, 2007) and the water-soluble drug tramadol (Zhang et al., 2000), enteric release formulations of diclofenac sodium (Lin and Kao, 1991), a taste masked formulation of the water insoluble macrolide antibiotics erythromycin and clarithromycin (Zgoulli et al., 1999). Spray drying has been used as for the formulation of co-processed excipients for direct compression (Di Martino et al., 2001; Gonnissen et al., 2007) and to formulate amorphous drugs with higher solubility (Ambike et al., 2005; Pandya et al., 2008).

Desai, (2007) used spray dried aqueous dispersions to prepare microparticles intended for controlled delivery of diclofenac sodium. High-amylose corn starch (HACS)-pectin blend polymers was used as a controlled release system. The mean particle size of various formulations was found to be in the range 5.8-7.3μm. The drug release was characterized by Fickian diffusion with a burst release of approximately 40% after 1 hour. The drug release was sustained up to 6 hours.

Zhang et al., (2000) showed that spray drying is a feasible technique for the formulation of sustained release microcapsules of tramadol resin complex (TRC) prepared using ethylcellulose as a controlled release polymer and various organic solvents including ethanol and ethylacetate. *In-vitro* dissolution studies carried out in 0.1M HCl suggested that 40% of the drug was released after 1 hour. The addition of diethyl phthalate resulted in better sustained release properties of ethylcellulose with approximately 30% of the drug released after 1 hour.

Lin and Kao, (1991) developed enteric coated microparticles of the poorly water-soluble NSAID drug, diclofenac sodium, by a spray drying technique. Sodium diclofenac was dispersed in an aqueous suspension comprising Eudragit L30D, PEG 6000 as a plasticizer, aerosil, soluble starch and lactose and was subjected to spray drying. Drug content was found to be in the range

64.05 - 91.76% when the eudragit was used in the range 3.75 - 26.25%. During dissolution studies, in acidic pH, lower drug release indicated efficient enteric coating, while in pH 6.8, 100% of drug was released within 1 hour for all the formulations, showing that the sodium diclofenac was successfully enteric coated.

Zgoulli et al., (1999) demonstrated that a single step spray drying technique can be successfully used to process microparticles of less than 80μm size without organic solvents or the use of multistep processes. Spray drying was also found to be a feasible technique to microencapsulate water insoluble macrolide antibiotics erythromycin and clarithromycin to mask its unpleasant and bitter taste.

Spray drying has also been extensively used in the pharmaceutical industry for drying, granulation and for the formulation of directly compressible powders for preparation of uniform weight tablets. Gonnissen et al., (2007) demonstrated that spray drying aqueous solutions can be successfully used for the continuous production of directly compressible powders. Binary and ternary mixtures containing drug substances and carbohydrates prepared by co-spray drying demonstrated the efficiency of erythritol, maltodextrin or mannitol to improve the physical properties and compactability of acetaminophen. The spray dried mixtures containing mannitol were characterised as being non-hygroscopic, highly dense with good flow properties, resulting in the formation of high tensile strength tablets produced by direct compression.

Spray drying was used by Di Martino et al., (2001) to modify crystal properties of acetazolamide by recrystallization during spray drying, resulting in better compression properties leading to better consolidation of the tablet. Spray drying has also been used to enhance the solubility and hence bioavailability of poorly soluble drug, simvastatin. Ambike et al., (2005) used spray drying to enhance the solubility of simvastatin from 15μg/ml to 69μg/ml by forming

amorphous solid dispersions of simvastatin using dichloromethane as a solvent. Pandya et al., (2008) also attempted to increase the solubility of simvastatin (100μm) by spray drying a methanolic solution of (1:1) simvastatin and HPMC. The spray dried particles had spherical morphology. Simvastatin was found to be present in the amorphous form in these particles. Solubility studies carried out at pH 7 showed that the solubility of amorphous simvastatin was greater, at 1.74 mg/ml, compared to the solubility of the original crystalline simvastatin at 0.46 mg/ml.

The advantages of spray drying for microencapsulation of drugs have been well described in the literature. These include,

1. A simple, rapid, low cost, single-step process that is easily scalable.
2. Reliability, reproducibility, and possible control of particle sizes and drug release (Esposito et al., 2002; Palmeri et al., 1994).
3. Microparticles obtained by spray drying are usually organic solvent-free with respect to other preparation methods that often result in particles possibly contaminated by toxic organic solvents (Esposito et al., 2002; Palmeri et al., 1994).
4. Thermolabile core substances can be coated by spray drying because exposure to elevated temperature is very short, normally ranging from 5 to 30 seconds. In addition, moisture sensitive drugs can be encapsulated by using non-aqueous coating systems.

The major disadvantages of spray drying is the loss of fine particles having a size smaller than several micrometers, which are not caught by the collector but are discharged with exhaust air resulting in a low product yield. When encapsulation is carried out on a laboratory scale the yield may be as low as 50% (Kond, 1979).

Spray drying has been used to prepare taste masked microparticles of water insoluble drug famotidine (Mizumoto et al., 2008; Xu et al., 2008) and

amorphous solid dispersions of poorly soluble drug perphenazine (PPZ) (Laitinen et al., 2009) for incorporation into FDDTs.

Famotidine particles prepared by spray drying a suspension of famotidine in an aqueous dispersion of ethylcellulose was found to be in crystalline form, with particle size below 150μm, a size suitable for incorporation into FDDTs.

Xu et al., (2008) attempted to prepare orally disintegrating tablets by direct compression of taste-masked microspheres of famotidine prepared using spray drying. The ODTs disintegrated in the buccal cavity within 30 seconds with an improved taste.

Spray drying was used in this thesis to prepare sustained release microparticles of sodium diclofenac and solid dispersions of simvastatin for formulation into FDDTs.

1.3. Model drugs used in the thesis

1.3.1. Diclofenac sodium

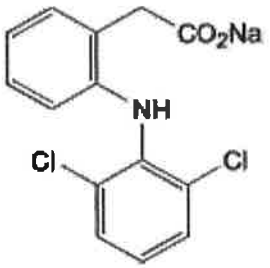
Diclofenac sodium (DFS) is a synthetic nonsteroidal anti-inflammatory drug (NSAID). DFS is an odourless, white to off-white, slightly hygroscopic powder. Diclofenac is a weak acid (pKa, 4.0) with a partition coefficient of 13 in octanol/phosphate buffer (pH, 7.4), while The log Poctanol/water of diclofenac sodium is 0.70. Sodium diclofenac is a slightly soluble drug with an aqueous solubility of 1.113 mg/ml (Llinàs et al., 2007).

DFS is used to treat minor aches and pains associated with the common cold, headache, muscle aches, backache, and arthritis. It is also used to reduce fever and is also commonly used for the short- and long term treatment of rheumatic disorders such osteoarthritis and ankylosing spondylitis. The

potassium salt, which is faster acting, probably due to its higher solubility compared to its sodium salt, is indicated for the management of acute pain.

Chemically diclofenac sodium is sodium 2-[(2,6-dichlorophenyl)amino] phenyl]acetate. The empirical formula of diclofenac sodium is $C_{14}H_{10}Cl_2NNaO_2$ and its molecular weight is 318.13. It is numerically identified by Chemical Abstract Service (CAS) registry number 15307-79-6. The structural formula of diclofenac sodium is outlined below in Figure 1.8.

Figure 1.8: Structural formula of diclofenac sodium



Diclofenac sodium is reported to cause GI side effects therefore it is commercially available as Diclac immediate release (IR) tablets containing 25 or 50mg and as Diclac prolonged release tablets containing 75 or 100mg DFS (Rowex Ltd., Bantry, Co. Cork, Ireland) (medicines.ie). DFS is safe to be administered as an immediate release (IR) formulation at low dosage strengths of 25mg, probably due to its rapid absorption after oral administration.

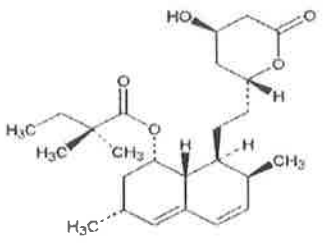
DFS is used as a model drug in this thesis for the formulation of IR and modified release (MR) FDDTs. FDDT formulations of the DFS would offer a convenient dosage form for the fast relief of pain to a wide range of patient populations including paediatric, elderly and active working people. In addition, to avoid a multiple dosage regimen, a modified release FDDT dosage form was also examined.

1.3.2. Simvastatin

Simvastatin (SIM) is a cholesterol lowering agent, used in the treatment of hypercholesterolemia and dyslipidemia. It belongs to the class of pharmaceuticals called "statins" and is derived from lovastatin. Simvastatin exists as a prodrug, i.e. in its inactive lactone form, which, after oral administration is hydrolyzed in the liver by cytochrome P450 3A4 to its active form, β,δ-dihydroxy acid. It acts by specifically and competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway, which catalyzes the conversion of HMG-CoA to mevalonate and inhibits the early and rate limiting step in the biosynthesis of cholesterol in the liver. In addition, simvastatin reduces very low density lipoprotein-cholesterol (VLDL) and triglycerides (TG), and increases high-density lipoprotein cholesterol (HDL-C) in the blood. It is used in the treatment of hypercholesterolemia and dyslipidemia, and to prevent cardiovascular disease, such as heart attack, stroke and peripheral vascular disease (Ismail, 2006; Kang et al., 2004; Patil et al., 2007).

Chemically, simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1,3,7®,8®(2S*,4S*),-8a®]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. It is numerically identified by Chemical Abstract Service (CAS) registry number 79902-63-9. The structural formula of simvastatin is outlined in Figure 1.9.

Figure 1.9: Structural formula of simvastatin



Commercially it is available as immediate release (IR) film coated tablets under the brand name Zocor® tablets marketed by Merck & Co. It is available as oval shaped tablets in 5 different dosage strengths (5mg, 10mg, 20mg, 40mg and 80mg). Simvastatin is orally administered in the therapeutic dosage range 5 - 80mg per day as a single dose in the evening. The maximum dose given is 80mg per day which is only recommended in patients suffering with severe hypercholesterolemia and facing a high risk of cardiovascular complications. Higher doses of 160mg have been found to be too toxic, while giving only minimal benefit in terms of lipid lowering. Following the patent expiry of innovator drug Zocor® in 2006, a number of generic tablet formulations have been developed and commercialised. In Ireland, generic simvastatin tablets are available as Simzor® film coated tablets (10mg, 20mg, 40mg), manufactured by Gerard Laboratories.

According to IMS Health (NYSE: RX, 2004), simvastatin is among the 20 leading prescription drugs in the United States, with approximately 15 million people in the United States taking a statin at any given time (Bottorff et al., 2003). Since 2004, simvastatin is also available as an OTC drug in a 10mg dose in certain countries like the UK. As simvastatin is particularly used by patients in the 40+ years of age who most probably are on a range of other medications i.e. for cardiovascular and diabetics conditions, patients compliance could be enhanced from an FDDT formulation.

1.4. Aims of the present work

Among the technologies reviewed above, lyophilisation provides highly porous matrices with fast disintegration time, however, unfortunately with low mechanical strength requiring specialised packaging and high cost of the process. The more conventional technique that involves a mixture of granulation and compression or direct compression is a cost efficient process however with adverse impact on the disintegration time. For fast disintegration

in general a low compression force has been utilised with resulting low mechanical strength. The issue of low mechanical strength was resolved by subjecting the tablets to temperature and humidity treatment. However, this is not applicable to heat and moisture sensitive actives and is a complex process which is not easily scalable and commercialisable.

The critical characteristics for good fast disintegrating tablets which have applications to a wide range of therapeutics and patient populations are low DT, and importantly high mechanical strength to allow suitable packaging, handling and storage so as to reach the patient in full integrity. In addition, a pleasant taste and good mouthfeel is desirable. A cost efficient process would be desirable for wide application and easy scale-up.

The novelty of this thesis is that we intend to devise a simple formulation to prepare FDDTs by a one-step direct compression process. While, previous technology such as Oralsolv® use multiple excipients for the preparation of FDDTs.

In this thesis, we examined the combined effects of formulation and process variables to formulate fast dissolving tablets with high mechanical strength, while maintaining the low disintegration time using the conventional tableting process, direct compression that is associated with a simple and cost effective and environment friendly process. While previous technology such as Orasolv® gives friable tablets thus requiring specialised packaging, Advatab® technology uses external lubrication to form rigid FDDTs, thus adding an additional step to the tabletting process. On the other hand, both, Oralsolv® and Advatab® requires strict humidity control during manufacturing and storage. The formulation in this thesis were put under stability at lab conditions of temperature and humidity.

The influence of a range of direct compression fillers and disintegrants of various mechanisms of disintegration on the mechanical properties and disintegration time were examined. Process variables including increase in compression force, tablet diameter, tablet weight and tableting speeds on the tablet characteristics were studied (Chapter 3). We intend to apply the selected formulations, based on their mechanical strength and DT, to formulate 2 hydrophobic model drugs, sodium diclofenac and simvastatin.

Modified release micoparticles of diclofenac sodium (DFS) were prepared by a spray drying technique. Subsequently, the influence of the incorporation of DFS and modified release (MR) DFS microparticles on the characteristics of the FDDTs was evaluated. Formulations were tested as part of a preclinical palatability study in dogs (Chapter 4).

The influence of incorporation of a second model drug, simvastatin API, a hydrophobic drug with higher log P of 4, on the characteristics of FDDTs was evaluated using selected/preferred placebo formulations from chapter 3. The influence of formulation and process parameters on the tablet characteristics was evaluated.

Subsequently, simvastatin was prepared as crystalline solid dispersions (SDPs) in a superdisintegrant matrix in order to enhance its rheology and dispersibility properties. Compression of SDPs into tablets was also investigated.

Finally, the aim was to validate the process and formulation developed for industrial application by studying the scalability, stability profiles of four simvastatin FDDT formulations. The results are presented in chapter 6.

CHAPTER 2

Materials & Methods

2.0 Materials

The materials used for the formulation and analysis of Fast Disintegrating Dissolving Tablets (FDDTs), controlled release diclofenac sodium (DFS) microparticles and preparation of solid dispersions (SDP) of simvastatin (SIM) are listed below in Table 2.1.

Table 2.1: List of materials used in the formulation and analysis of FDDTs, controlled release diclofenac sodium microparticles and simvastatin SDP

Material	Supplier
Acesulfame® K (Sunnett)	PhEur, USP, Nutrinova, Germany
Acetonitrile	HPLC grade, Sigma-Aldrich and Lennox, Ireland
Aerosil® 200	GMP, Degussa GmbH, Germany
Chocolate flavour	Food grade, Cadbury, Ireland
Citric acid (anhydrous)	USP, Leochem, China
Deionised water	Elgastat, England, UK.
Diclofenac sodium (DFS)	USP grade, Dipharma Francis, Italy
Ethanol (EtOH)	Reagent grade, Lennox, Ireland
Ethylcellulose (EC) (45cP)	USP, Sigma-Aldrich, Ireland
Explotab®	JRS Pharma, Germany
Glacial acetic acid	Reagent grade, Sigma-Aldrich, Ireland
Kollidon® CL-SF	PhEur, USP, BASF, Cheshire, UK
Lactose based co-processed (Ludipress®)	BASF, Cheshire, UK
Luquasorb®1280	GMP, BASF, Cheshire, UK
Lutrol® F127 (Poloxamer 407)	USP, BASF, Cheshire, UK
Magnesium Stearate	PhEur, JMB, UK
Manganese (IV) oxide	Sigma-Aldrich, Ireland
Mannitol 200 (Parteck®) (Merck KGaA)	PhEur, BP, USP, Norman Lauder, Dublin

Mannitol 300 (Parteck®) (Merck KGaA)	PhEur, BP, USP, Norman Lauder
Mannogem™ EZ	PhEur, USP, SPI Pharma, Newcastle, DE
Monobasic sodium phosphate	Sigma-Aldrich, Ireland
Novamint fresh peppermint	GMP, S Black Ltd, Herts, UK
Prosolv® HD90	PhEur, JRS Pharma, Ireland
Raspberry flavour	GMP, S Black Ltd, Herts, UK
RxCIPIENTS™ FM1000 (Calcium Silicate)	GMP, Huber engineered, Finland
Simvastatin (cGMP)	USP grade, Leo Chemical, China
Simvastatin (HPLC grade, S6196-5mg)	Sigma-Aldrich, Ireland
Sodium hydroxide	Sigma-Aldrich, Ireland
Sodium dihydrogen orthophosphate	Sigma-Aldrich, Ireland
Sodium dodecyl sulfate	Sigma-Aldrich, Ireland
Sodium acid phosphate	Sigma-Aldrich, Ireland
Sodium phosphate	Sigma-Aldrich, Ireland
Sodium chloride	Sigma-Aldrich, Ireland
Sodium citrate (anhydrous)	USP, Leochem, China
Sorbitol 400 (Parteck®) (Merck KGaA)	PhEur, BP, USP, Norman Lauder, Dublin
Tween 20	Sigma-Aldrich, Ireland
Vanilla Cream favour	GMP, S Black Ltd, Herts, UK
Zocor® tablets (10mg, 20mg, 80mg)	United drug, Ireland
Syringe, 2mls and needles	Fannin Healthcare, Ireland
0.45µm hydrophilic PVDF filter	Millipore Millex - HV
0.45µm membrane filters (Polyamide)	Schleicher & Schuell, Germany
85% phosphoric acid	Sigma-Aldrich, Ireland
HPLC vials (clear, 2mls)	Apex scientific, Ireland
C18 column, 5micron, 250x4.6mm	Apex scientific, Ireland
Glass Vials 10.5ml snap top rolled rim	AGB scientific, Ireland

2.1. Methods

The methods used for the formulation and characterisation of fast disintegrating dissolving tablets (FDDTs), spray dried microparticles of sodium diclofenac and solid dispersions of simvastatin are outlined below.

2.1.1 Formulation of fast disintegrating dissolving tablets (FDDTs)

The formulation of all FDDTs was carried out in the following three distinct steps, as described below:

1. Dispensing of ingredients

All materials were dispensed in the required amounts as per the composition of each batch. The tableting ingredients were accurately weighed on a Sartorius CP2202S balance (Bradford, MA, USA) and dispensed into a plastic resealable bag.

2. Preparation of tableting blend

The weighed ingredients in the powder form except for magnesium stearate were manually blended together by horizontal and vertical shaking in a resealable plastic bag using geometric dilution where required. After initial dry powder blending for a period of 5 minutes, magnesium stearate was added and tablet blend was further blended gently for approximately 1-2 minutes. The tablet blend weight used for the small scale manufacture was 25g, for scale-up batches, the tablet blend weight was 100-150g to allow sufficient tablets for stability studies.

3. Compression of blend into tablets

The prepared dry powder blend was transferred to the hopper of an 8 Station Riva piccola Rotary tablet press (Riva Piccola, Hants, UK). Tablets were compressed at a tablet turret speed of 7rpm, 28rpm or 49rpm. A range of tooling configurations was used to give either flat faced bevelled edge tablets of diameter 10-15mm or biconvex tablets of diameter 10 and 13mm (Table 2.2). Tablets were compressed at the target tablet weight of 150mg to 800mg/FDDT, depending on the tooling size used. Tablets were compressed

at the compressional forces of 70MPa (7kN) - 200MPa (20kN). All tablets formulated were characterised for their mechanical properties, drug content, dissolution and drug release properties.

Table 2.2: Tooling configurations and sizes used in the formulation of FDDTs

Tooling diameter (mm)	Tooling shape	Target tablet weight (mg)
10	Round, Flat faced bevelled edge (FBE)	150/200/300
13	Round, Flat faced bevelled edge (FBE)	300/500
15	Round, Flat faced bevelled edge (FBE)	500
20	Round, Flat faced bevelled edge (FBE)	1000
10	Biconcave (BC)	200/300
13	Biconcave (BC)	300/500

2.1.2 Preparation of controlled release diclofenac sodium microparticles

The required amounts of ethylcellulose (EC) and diclofenac sodium (DFS) were weighed and dissolved in ethanol to give feed solutions containing 10%w/v of total solid content containing the DFS and EC at a weight ratio of 1:3. The ethylcellulose was first dissolved in ethanol using a magnetic stirrer (Yellowline, MSC basic C, IKA works, USA) at a stirring speed of 600 - 1000rpm for 20-30 minutes. The appropriate amount of DFS was then added to the EC solution and stirred using the same stirring speed, until complete dissolution of the drug. Batch sizes prepared ranged from 50ml to 100ml. The microencapsulation of DFS with EC was carried out using a Buchi Mini Spray dryer, Model B-290 (Buchi Switzerland) in the closed loop mode. The polymer/drug solution was spray dried under nitrogen using the following settings: Buchi peristaltic pump setting at 16% - 36% corresponding to a feed flow rate of 4 - 9.6ml/min, compressed nitrogen flow at 473Nl/h - 357Nl/h (40-30mm), inlet temperatures of 80 - 110°C, and aspirator setting of 65 - 91% (26

- 35m^3/h). the spray drying parameters emplyed for each batch is outlined in Table 4.1, Chapter 4. A two fluid nozzle equipped with 0.7mm tip size, and 1.5mm cap size was used.

The resultant microparticles were recovered, weighed and the percent product yield calculated using the equation 2.1 below:

$$Percentage\,Yield = \left(\frac{weight\ of\ microparticles}{weight\ of\ polymer + drug} \right) x100 \qquad \text{(eq.2.1)}$$

Microparticles formulated were stored in sealed glass vials (AGB scientific, Ireland) until further characterisation.

2.1.3. Preparation of solid dispersions (SDP) of simvastatin

Solid dispersions (SDP) were prepared by a conventional spray drying technique, using a Buchi Mini Spray Dryer, B290 (Buchi, Switzerland). The spray dryer was operated in an open loop mode, suitable for aqueous solvents. Simvastatin alone or in combination with one of the following three carriers; polyvinylpyrrolidone, crosslinked (crospovidone) i.e. Kollidon CLSF (K-CLSF), sodium starch glycollate (Explotab; SSG), and calcium silicate (CaS) was formulated as an aqueous dispersion (feed dispersion) containing 7.5%w/v of total solids at drug to carrier weight ratio of 1:1.

The feed solutions were prepared by accurately weighing the appropriate amount of the carrier using a Sartorius balance, Model CP225D (Bradford, MA, USA) and adding this to 50ml of deionised water (DI) in a closed Duran bottle. This mixture was stirred for 20-30 minutes at 500 - 600 rpm using a magnetic stirrer, (Yellowline, MSC basic C, IKA works, USA), until a solution or homogenous dispersion of the carrier was formed. The required quantity of simvastatin was then accurately weighed and added to the resultant

solution/dispersion and stirred for a further 20-30 minutes at the same stirring speed, to allow complete dissolution/dispersion of the drug. Batch size of 50mls was used for each batch prepared.

The feed solutions were spray dried using the following settings: Buchi peristaltic pump setting at 4-16% corresponding to a feed flow rate of 1.0 - 4.0 ml/min, compressed air flow at 414Nl/h (35mm), inlet temperature of 90°C, and air aspirator setting of 100% (40m^3/h). The spray drying outlet temperature was monitored.

The resultant solid dispersions were recovered, weighed and the percentage product yield was calculated using the below equation 2.2

$$Percentage\,Yield = \left(\frac{weight\,of\,solid\,dispersions}{weight\,of\,drug + carrier} \right) x100 \qquad \text{(eq. 2.2)}$$

2.1.4. Characterisation of FDDTs

The tablets formulated were subjected to various tests as described in the requirements for tablets and fast dispersible tablets in the British Pharmacopoeia (BP, 2008a; PhEur, 2002). However, due to the relatively small scale batches, the number of tablets tested in certain cases was reduced and these are noted in individual test method described below.

2.1.4.1. Uniformity of weight (mass)

Uniformity of tablet weight was carried on n=10 tablets. Ten tablets were taken at random and weighed individually on a Sartorius balance, Model CP225D (Bradford, MA, USA). The average mass of the FDDTs +/- standard deviation were calculated. For the batch to pass the test of weight uniformity the percentage deviation allowed as per the specifications in the B.P. 2008 (BP, 2008a) is outlined in Table 2.3.

Table 2.3: Percentage deviation allowed for weight variation test of tablets (BP 2008)

Average weight	Percentage deviation (±)
≤ 80mg	10
> 80mg and < 250mg	7.5
≥ 250mg	5

2.1.4.2. Mechanical strength of tablets

Mechanical strength of the tablets is designed to evaluate the durability of the tablet to withstand the mechanical shocks during production, packaging, shipping and use. Therefore, it is a critical attribute dictating packaging requirements for the tablets to reach the patient in an intact form. The hardness (H) or tensile strength (TS) of the tablets was measured as described below. Tensile strength for the tablets was calculated using the equation 2.3.

2.1.4.2.1. Hardness/Crushing strength

The breaking force or Hardness (H) or crushing strength (CS) is a measure of the load at which the tablet breaks under diametrical compression between two flat jaws. This test was carried out individually on n=10 tablets using a pre-calibrated PTB 411E Tablet hardness tester (PharmaTest Germany). The instrument is generally calibrated every year by the the equipment provider. Individual tablets was placed between the jaws and the force (Newtons) needed for the diametrical crushing of the tablets was recorded. The average hardness/crushing strength +/- standard deviation was then calculated (BP, 2008a).

2.1.4.2.2. Tensile strength of tablets

Tensile strength is a fundamental measurement of resistance to fracture. It is defined as bond strength of tablets. The use of tensile strength allows the dimensions of the compact to be taken into account, which is in contrast to the use of crushing strength. The tensile strength of a tablet is usually measured by diametric compression. Under correct conditions of loading, the diameter of the tablet is subject to a uniform load that causes failure. Despite the load being uniform across the diameter, it is frequently found that the initiation of the fracture is in the center of the compact and that the crack formed does not extend completely to the outer diameter. The measured tensile strength may thus be an indicator of bonding conditions of the tablet. The tensile strength was calculated from the measured crushing strength, using equations 2.3 (Heinz et al., 2000).

$$\sigma_{tensile} = \frac{2.F_{failure}}{\pi.A_{cross-sectioned\ area}} \qquad \text{(eq 2.3)}$$

Where, $F_{failure}$ = hardness/crushing strength for tablets

For biconvex tablets, the cross-sectioned area was calculated by using equation 2.4 (Heinz et al., 2000).

$A_{cross\text{-}sectional\ area}$ = 2 x (surface area of upper/lower spherical caps) + area of cylinder**

$$= 4\,\pi Rh + 2\,\pi a \cdot b \qquad \text{(eq 2.4)}$$

Where,

a = radius of tablet,

h = height of spherical cap,

R = the radius of circle from which spherical cap was obtained, and

b = height of tablet edge

** is the area of the cylinder without top and bottom, (as the top and bottom was included in cup area), i.e. its area of the belly band - only central part of the tablet, excluding the cups

For flat faced, bevelled edge tablets, the cross-sectioned area was calculated by using equation 2.5,

$A_{cross\text{-}sectional\ area}$ = 2 x (Cup area*) + Area of the belly band

= 2 x ([area of the central part of the cup (cylindrical)] + area correction) + $2\pi rh$**

$= 2 \times ([2\pi r_1^2 + 2\pi r_1 h_1] + bh_1/2) + 2\pi rh$ (eq 2.5)

Where,

r_1 = radius of upper/lower cup

h_1 = the height of upper/lower cup

b = base of the upper/lower cup (excluding the central cylindrical part)

r = radius of the belly band

h = height of the belly band

* cup area was provided by Natoli Engineering Company, Inc, Missouri, USA

** is the area of the cylinder without top and bottom, (as the top and bottom was included in cup area)

2.1.4.3. Friability test

Friability test on tablets was performed on n=10 tablets, lower than the number of tablets required according to B.P. 2008, (BP, 2008a) test method which recommends a sample of whole tablets corresponding as near as possible to 6.5g for tablets equal to or less than 650mg in weight. The test was carried out using a pre-calibrated PTFE Friability tester, (PharmaTest Germany). The tablets were carefully de-dusted prior to testing accurately weighed and placed in the drum of the friability tester and the drum was allowed to rotate 100 times. The tablets were then removed carefully from the friabilator, dedusted and re-weighed accurately. A maximum loss of tablet mass, not greater than 1.0 per cent was considered acceptable. The test was run once. If tablets cracked, cleaved, or broke after testing, the sample was recorded as "failed the friability test".

2.1.4.4. Disintegration test

The disintegration tests were performed in deionised water as disintegration medium maintained at a temperature between 37°C ± 2°C, using a pre-calibrated Pharmatest PTZ Auto, PTFE Disintegration tester, (PharmaTest Germany). The tablet was believed to be disintegrated only after all the dispersed tablet fragments passes through the 2.0 ± 0.2mm mesh apertures of the disintegration apparatus.

The disintegration time of tablets formulated in this thesis was determined using 2 test methods as described below,

Method 1: A modification of the BP 2008 method for conventional tablets was used. Only one tablet at a time was placed into the disintegration apparatus and the time taken (seconds) for the tablet to fully disintegrate was recorded. The test was repeated with 5 additional FDDTs.

Method 2: As per the BP 2008 method for oral lyophilisate, only 1 tablet was placed in a beaker containing 200 ml of water at a temperature of 15-25°C the time taken for FDDT to fully disintegrate was recorded. The test was repeated on another 5 FDDTs (PhEur, 2002). A representative picture for the end point of the disintegration of the tablet is presented below in Figure 2.1.

Figure 2.1: End point for the disintegration test (Method 2) carried out as per the BP 2008 method

2.1.4.5. Tablet thickness

The thickness of each FDDT (n=10 tablets) was measured using a pair of calibrated digital vernier callipers (digital Caliper Workzone, UK). The average thickness of the FDDTs and standard deviation was calculated.

2.1.4.6. Porosity of tablets

The porosity of the tablets (ε) was calculated using equation 2.6 (Sugimoto et al., 2006b):

$$\varepsilon = (1 - \frac{m}{\rho_{true} v}) \times 100 \qquad \text{(eq 2.6)}$$

Where,

ρ_{true} = true density of the tableting mixture

m = weight of the tablet

v = volume of the tablet.

The true density of the materials was determined using a helium pycnometer, (Accupyc 1330, V3.03, Micrometrics, Norcross, USA). The experimental sample was accurately weighed and loaded into the sample cell. The sample volume was computed by measurements of the pressure observed by filling the sample chamber with pure helium gas followed by discharging the gas into a second empty chamber up to 10 purges. The measurement was carried out at 25-27°C. The measurements were repeated for 5 such cycles.

Calculation for the Volume of tablets

a. For flat faced bevelled edge tablets

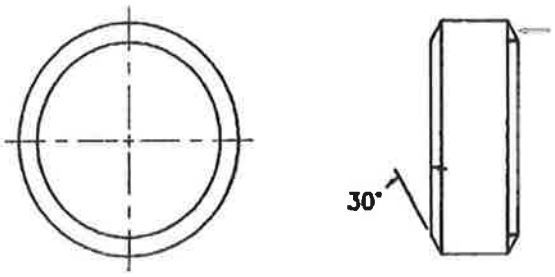


Figure 2.2: Flat faced bevelled edge tablets

Volume of flat faced bevelled edge tablets,

= 2 x (Cup volume)* + (volume of the belly band)

= 2 x (volume of central (cylindrical) part of the cup + volume correction) + (surface area of the round x belly band thickness)

$= 2 \times (\pi r^2 h + [bh/2\ (\pi d)) + \pi r_1^2 (h_1)]$ (eq 2.7)

Where,

r = radius of the upper/lower cups,

h = height of upper/lower cups,

b = base of the outer part for volume correction,

d = diameter of the upper part of the cup,

r_1 = radius of the belly band,

h_1 = height of the belly band

* cup volume was provided by its manufacturer, Natoli Engineering Company, Inc, Missouri, USA.

b. For biconvex tablets

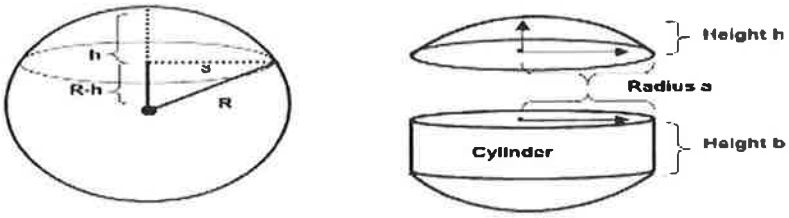


Figure 2.3: Biconvex tablets

The volume of a biconvex tablet can also be derived as below (Pérez-Ramos et al 2005),

Because the volume of the spherical cap is:

$V_{spherical-cap} = 1/6\ \pi h\ (3a^2 + h^2)$

And the volume of the cylinder is:

$V_{cylinder} = \pi a^2 \cdot b$

Then, the overall volume occupied by the tablet is:

$V_{Tablet} = 2/6\ \pi h\ (3a^2 + h^2) + \pi a^2 \cdot b$

However, the height of the tablet edge *b* does not depend solely on the geometry of the punch but also on the distance traveled by the punches inside the die during compaction. This dimension may not be generally measured by formulators who prefer to measure the total thickness (T_{face}) of the tablet. In this case, the height of the band is calculated from the total face thickness (T_{face}) measured:

$b = T_{face} - 2h$

Rearranging and gives:

$$V_{Tablet} = 2/6\ \pi\ h\ (3a^2 + h^2) + \pi a^2 \cdot (T_{face} - 2h) \quad \text{.....(eq 2.8)}$$

This equation allows the volume of a tablet to be computed directly from tablet measurements.

2.1.5. Characterisation of microparticles and solid dispersions

Controlled release diclofenac sodium microparticles and solid dispersions of simvastatin were subjected to various tests of characterisation as outlined below.

2.1.5.1 Particle size analysis (dry and wet method)

The particle size and size distribution of active, microparticles and spray dried solid dispersions were measured by laser diffraction analysis using a Mastersizer 2000 (Malvern Instruments, U.K.). The microparticles/solid dispersions were measured for size either in the dry state using the dry dispersion attachment (Scirocco™) or by the wet dispersion technique that uses the Hydro SM™ cell. Particle size analysis of the active was carried out in the dry state only. Briefly, a small amount of sample, was placed onto the sample tray of the dry powder cell and the derived diameters D10%, D50%, D90% were measured using the following protocol. D10% tells that 10% of the volume distribution is below this value. Similarly, is D50% and D90%.
Result range: 0.02 - 2000μm, Particles refractive index: 1.50, Result calculation mode: General purpose, measurement time: 3 seconds, measurement snaps: 3000, Background time: 12 seconds, background snaps: 12000, vibration feed rate: 80%, dispersive air pressure: 2bar. This measurement was replicated for 2 further aliquots to give n= 3 measurement of each sample. The average D10%, D50%, D90% and Span +/- SD were

then calculated for each sample. The span value (d90-d10/d50) is an indicative of the width of the particle size distribution, which when small (< 2) reflects a more homogeneous particle size distribution.

The feed dispersions used for the preparation of solid dispersions of simvastatin were measured for the particle size by wet method. The dispersed sample was then added to water in the Hydro SM™ system and particle size and size distribution measured using the following setting:

Dispersant: Water, Refractive index: 1.33, Measurement time: 3 seconds, Measurement snaps: 3000, Background time: 12 seconds, Background snaps: 12000, Dispersion unit controller - stirring speed: 1260 rpm.

The measurement in each case was carried out in triplicates and the average particle sizes; D10%, D50%, D90% and Span +/- SD were calculated.

2.1.5.2. Evaluation of Morphology by Scanning Electron Microscopy

The morphology of the diclofenac sodium and simvastatin as received and as microparticle or solid dispersion formulations was determined using a Variable Pressure Field Emission Scanning Electron Microscope (Hitachi S-4300 Field, USA or Tescan Mira (Tescan USA)).

Samples were mounted onto stubs using double sided adhesive tape and were coated with a thin layer of gold. The coated specimen was then examined under the microscope at various magnifications and photographed at an appropriate magnification of 500x to and 5000x.

2.1.5.3. Rheology

Rheological properties of the drug raw material, diclofenac sodium and simvastatin were determined by two methods, a) Carrs index and b) angle of repose.

2.1.5.3.1. Carr's compressibility index

Rheological properties of the diclofenac microparticles and simvastatin solid dispersions were determined by measuring the bulk and tapped densities of the samples and calculating their Carr's Compressibility index (CI). The bulk and the tapped density of each sample were first determined in triplicate as described below (BP, 2008a).

The bulk density (ρ_{bulk}) of simvastatin, spray dried simvastatin dispersions and diclofenac microparticles were determined by measuring the poured volume of a weighed amount of the sample (2.0g) in a volumetric cylinder. The cylinder was lightly tapped once to collect all the powder sticking on the wall of the cylinder. The tapped density (ρ_{tapped}) of the spray dried powders was achieved by mechanically tapping the graduate cylinder as per the method described in BP 2008, using a tapped density volumeter (Copley Instruments, Nottingham, UK). The taps were carried out at following three intervals 10, 500 and 1250 taps and the corresponding volumes V_{10}, V_{500} and V_{1250} were read to the nearest milliliter. Volume readings were taken until little further volume change was observed. The volume of the sample was used in the calculation of the tapped density. Analysis was carried out in triplicate and reported as average and +/- standard deviation.

The Carr's compressibility index (CI) was calculated from the measured values of bulk and tapped densities of the powder, using equation 2.9.

$$CI = 100\ x \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \qquad \text{(eq 2.9)}$$

where ρ_{tap} and ρ_{bulk} are tapped and bulk densities, respectively.

The CI may be interpreted by the generally accepted scale of flowability outlined in the BP 2008 and is illustrated below in Table 2.4.

Table 2.4 Scale of flowability

Compressibility index (%)	Flow character
1-10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
> 38	Very very poor

2.1.5.3.2. Angle of repose

Prior to measuring the angle of repose, the material discharge (drop height) was determined such as to form a conical pile with minimum pile disturbance. A funnel of slope 58.56° to the vertical axis and orifice opening of 4.91mm was positioned on the stand with the height maintained at approximately 2-4cm from the top of the powder pile as it is being formed in order to minimize the impact of powder falling on the tip of the cone (BP, 2008a).

A predefined mass (2.0g) of the drug was poured through the funnel and the angle of repose of the heap was calculated by measuring the height of the cone of powder and the diameter of the base of the cone. The angle of repose, α, is calculated from the equation 2.10:

$$\tan\alpha = \frac{height}{0.5\,x\,base} \qquad \text{(eq 2.10)}$$

The flowability of the sample was interpreted as per the BP 2008 and is outlined in Table 2.5

Table 2.5 Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (°)
Excellent	25-30
Good	31-35
Fair–aid not needed	36-40
Passable–may hang up	41-45
Poor–must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

2.1.5.4. Thermal analysis

The thermal behaviour of the drug, polymer/carrier, physical mixtures drug + polymer/carrier and corresponding microparticles/solid dispersions was determined.

Differential Scanning Calorimetry (DSC) was carried out to evaluate polymorphic nature and any phase transition of the drug, carrier and drug/carrier physical mixtures and corresponding spray dried forms, whereas Thermogravimetric Analysis (TGA) was carried out for the purpose of determining the residual moisture or solvents in the native drug and its product(s). It is also indicative of degradation of the drug.

2.1.5.4.1 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry was conducted using a DSC Q100 V9.0 Build 275, with a recirculation cooling system (TA Instruments, New Castle, Delaware, USA). The analysis was performed under a purge of dry nitrogen (50ml/min). Aliquots of the drug or product were accurately weighed, and sealed in aluminum pans. Sample weights varied between 1 - 5mg. Samples

were heated by a ramp method to a temperature of 300°C - 350°C (for diclofenac sodium and its products) or 200°C (for simvastatin and its products), at a heating rate of 10°C per minute. An empty aluminum pan was utilized as the reference. Calibration and validation of the instrument was performed with indium reference standard prior to the start of the study. Wherever indicated, each sample was subjected to two heating cycles, interrupted by a cooling phase by a ramp method. The second cycle was aimed at verifying the glass transition temperature. Thermal events, indication of glass transition, melting, recrystallization or solvent evaporation were recorded. The glass transition temperature (Tg) was defined as the midpoint of the transition and the melting points were reported as onset, end and peak temperature of the endothermic process.

2.1.5.4.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was conducted to investigate the percentage of residual moisture of solvent present in the product. TGA was performed using a TGA Q50 V6.3 Build 189 (TA Instruments, New Castle, Delaware, USA) under a nitrogen atmosphere. Samples were loaded onto open aluminium pan and heated at a rate of 10°C per minute, to a temperature of 250°C for diclofenac sodium and 200°C for simvastatin. The TGA was precalibrated using standard weights of 100mg and 1000mg as per the in built TGA software protocol.

2.1.5.5. X-ray powder diffractometry (XRPD)

The XRPD studies were performed to determine crystallinity, polymorphic or amorphous nature of the drug alone and its products. XRPD analysis was also carried out on the drug, physical mixtures of drug and carrier at various drug to carrier ratios as well as on the spray dried formulations. The XRPD patterns of all the samples were obtained using a Bruker D8 Discover instrument. Each sample was placed and flattened with a glass slide to obtain

a good surface texture and inserted in the cavity of an aluminum sample holder. The sample holder and detector were moved in a circular path during measurement of the powder pattern, to determine the angles of scattered radiation and to reduce preferred sample orientation.
The samples were irradiated with monochromatized Ni filtered CuKa anode radiation (01542nm). Samples were analysed using a step width of 0.02^{o} and 2θ between 2 to 40^{o} 2θ, at ambient temperature.

2.1.5.6. Hot stage microscopy (HSM)

Hot stage microscopy (HSM) was used to understand and support the melting events that occurred during the DSC analysis. HSM was carried out using an Olympus BX51 (Olympus Optical Co. Ltd., Tokyo, Japan) polarizing optical microscope equipped with a Linkam LTS350 hot stage (Linkam Scientific Instruments Ltd., Surrey England) and Linkam TMS94 programmable temperature controller. Pure simvastatin and SDP were placed on a glass slide, and gradually heated from room temperature at $5^{o}C$/min up to $200^{o}C$. The heating rate was maintained at $5^{o}C$/min to carefully picture the events taking place during the analysis. Photographs were taken using Olympus C-7070 Digital Camera (7.1megapixel, 4x optical zoom), at room temperature and whenever thermal events were observed. The photographs/observations were correlated with thermal events observed by DSC.

2.1.5.7. Fourier Transform Infra-Red (FT-IR) spectroscopy

FT-IR spectra were obtained using a Bruker Tensor 27 FT-IR spectrometer (Bruker. Optics, Ettlingen, Germany) equipped with DTGS detector. The background scan was performed prior to analysis. The spectra were an average of 16scans at a resolution of $4cm^{-1}$ over the frequency range of 4000 - $400cm^{-1}$. KBr discs were prepared using a manually operated hydraulic press (Specac, Kent, UK).

Analysis of the spectra was performed using the OPUS Data Collection Program (V 1.1).

The samples for infrared analysis and the KBr were dried for at least an hour prior to analysis in a drying oven (Specacabinet, Kent, UK) at 32 ± 0.5°C.

In the present study, FT-IR was used to determine potential interactions between the drug and various carriers employed in the formulation of various solid dispersions. FT-IR spectra derived for the SDP were compared with that of the physical mix and the pure components present in the SDP.

2.1.5.8. Analysis of drug content in diclofenac sodium formulations

The content of diclofenac sodium in various formulations was analysed using an Ultraviolet visible (UV-vis) spectrophotometer (Libra S22 UV/Visible Spectrophotometer, Biochrom, UK) at an absorbance of 276nm.

A calibration curve for DFS was first prepared in phosphate buffer saline (PBS) pH 7.4, for drug assay studies (Kincl et al., 2004) and in PBS pH 6.8 to allow drug measurement during drug release studies (Barakat and Ahmad, 2008).

A stock solution of DFS of 0.1mg/ml concentration was prepared in triplicate, by dissolving 10mg of diclofenac sodium in 100ml of either PBS pH 7.4 or pH 6.8. A series of dilutions was prepared to give a range of concentrations from 0.02mg/ml to 0.1mg/ml. The absorbance for each concentration was measured at 276nm using a UV/VIS spectrophotometer. The absorbance was plotted against concentration (mg/ml) at each pH of 7.4 and 6.8 and fitted using linear regression analysis.

The representative calibration equations for the calibration curve at pH 6.8 (eq 2.11) and pH 7.4 (eq 2.12) are given below and the calibration curves are shown in appendix 1. The correlation coefficient was found to be r^2= 0.9997 and r^2=0.9995, respectively, indicating an excellent linearity.

Calibration equation of DFS in PBS pH 6.8

$$Y = 34.654X + 0.0187 \qquad (r^2 = 0.9997) \quad \text{(eq 2.11)}$$

Calibration equation of DFS in PBS pH 7.4

$$Y = 35.276\,X + 0.022 \qquad (r^2 = 0.9995) \quad \text{(eq 2.12)}$$

Where, Y = absorbance and X = concentration (mg/ml)

1. Assay of DFS content in microparticles

Aliquots (n=3) of 100mg of microparticles were accurately weighed and dissolved in 2ml of ethanol using sonication for 15 - 30 minutes (Brason Ultrasonics, Danbury, CT, USA). 10ml of PBS pH 7.4 was added to this solution to precipitate the ethylcellulose polymer. After centrifugation at 5000rpm for about 20 minutes (Hettich Rotina 35R refrigerated tabletop centrifuge, DJB labcare, UK), 1ml of the clear supernatant was withdrawn and further diluted to 10ml with PBS pH 7.4. The concentration of diclofenac sodium in the diluted solution was measured at 276nm. The content of drug was calculated using the standard calibration curve equation 2.12.

The drug loading in the microparticles was calculated by using the following equation 2.13,

$$\%\ Drug\ loading = \left(\frac{amount\ of\ drug\ in\ microparticles}{weight\ of\ microparticles} \right) x100 \qquad \text{(eq 2.13)}$$

The encapsulation efficiency (EE) of DFS in the microparticles is defined as the percentage of drug entrapped in the microspheres with respect to the total amount of drug added during the preparation of microspheres. It was calculated using equation 2.14.

$$\%\ Encapsulation\ efficiency = \left(\frac{assayed\ drug\ loading}{theoretical\ drug\ loading} \right) x100 \qquad \text{(eq 2.14)}$$

2. Verification of the assay method used for assay of DFS content in microparticles

The DFS assay method was verified to ascertain that the polymer does not interfere with the DFS detection. Samples containing the polymer (EC) alone, and physical mix of EC and DFS at the weight ratio of 25:75 ratio were prepared using the method described above for the assay of DFS content of microparticles and were scanned over the range of 250nm to 400nm and UV absorbance at 276nm was measured. The UV scan for solutions from EC alone showed no absorbance over the 250-400nm range (Appendix 1), plus there was no absorbance at 276nm.

The UV scan of the physical mixture of ethylcellulose with diclofenac sodium showed one peak at a wavelength of 276nm, similar to the scan of DFS alone. The peak at a wavelength of 276nm is due to DFS used and similar to that reported in the literature (Adayeye CM, 1990).

As ethylcellulose does not absorb at 276nm it will not interfere with the determination of diclofenac sodium. In addition the assayed drug content from the physical mixture of DFS and ethylcellulose was 100% of the expected content demonstrating the ability of the assay method to measure correct amounts of drug.

3. Assay of DFS content in diclofenac sodium FDDTs

The DFS content of each batch of FDDT was determined using a modification of the method described above. Individual FDDTs (n=3) were weighed and ground using a mortar and pestle. All the powder for each tablet was dispersed in ethanol by sonicating for 15-30 minutes. This was followed by the addition of PBS pH 7.4 and centrifugation at 5000rpm for 20 minutes. The absorbance of the resultant supernatant sample was analysed for drug content at 276nm, measured by UV-vis spectroscopy. The DFS content was calculated using the standard calibration curve equation 2.12.

2.1.5.9. Drug release studies of diclofenac sodium microparticles

Drug release studies of the diclofenac sodium microparticles were carried out using an OLS200 shaking water bath (Grant, Keison products, UK), operating at a shaking speed of 100rpm. Aliquots (n=3) of 100mg of microparticles were accurately weighed and placed in stoppered conical flask each containing 100ml of PBS pH 6.8, previously equilibrated at 37°C. The conical flasks were placed in the shaking water bath maintained at a temperature of 37°C ± 0.5°C and at intervals of time from 30 minutes to 7 hours, 1ml of the dissolution medium was withdrawn and replaced with the fresh dissolution medium. The withdrawn sample was filtered, diluted to 10ml using fresh dissolution medium and assayed for the drug content by UV spectroscopy measurement at 276nm. The amount of DFS in each sample withdrawn was calculated using the calibration equation (equation 2.11). The cumulative DFS released at each timepoint was calculated to allow for correction of DFS removed at each sampling point.

2.1.5.9.1. Mathematical fit of drug release

To investigate the mechanism of drug release from the diclofenac sodium microparticles, the *in-vitro* drug release data was mathematically fitted to the equation 2.15 (Peppas, 1985; Ritger and Peppas, 1987; Siepmann and Peppas, 2001) which correlates drug release with time through a simple exponential equation, equation 2.15. This equation has been used to evaluate drug release from controlled release polymeric systems. It is particularly useful when the drug release mechanism is not well known or when there is more than one type of release phenomenon involved.

$$Q = k\,t^{n} \qquad \text{(eq 2.15)}$$

Where, Q is the cumulative amount of drug released at time t, k is the kinetic constant, and n has been proposed as release exponent, indicative of the

release mechanism. Values of $n \leq 0.43$ indicates Fickian release, while values of $n = 0.85$ indicates a purely polymer relaxation controlled delivery referred to as Case II release. Intermediate values ($0.43 < n < 0.85$) indicate an anomalous behaviour (non-Fickian kinetics), whereas $n > 0.85$ indicates super case II release, resulting from increased plasticization at the relaxing boundary, especially a gel layer.

The drug release profiles were fitted by linear or nonlinear regression method using statistical software, SPSS version 15.0 for windows (SPSS, Inc, Chicago, IL, USA). The coefficient of correlation (r^2) was used to evaluate the accuracy of the fit and the F-ratio probability was used to evaluate the suitability of the mathematical drug release model.

2.1.5.10. Analysis of simvastatin formulations

2.1.5.10.1. Analysis of drug content in simvastatin formulations

A HPLC method for the assay of simvastatin was set up using the method described in the (USP, 2007), under the section, "USP Monographs: Simvastatin tablets" or as per the method outlined in the BP 2008 for Simvastatin tablets (BP, 2008b). The mobile phase, column and conditions used are given below:

HPLC system: Perkin Elmer Series 200 Model S200 A/S

Mobile phase: A filtered and degassed mixture of acetonitrile and buffer pH 4.5 solution at the volume ratios of 65:35

Column: 250 x 4.6mm, Gemini 5µ C18 (A stainless steel column packed with octadecylsilyl silica gel for Chromatography)

Column temperature: 45°C

Flow rate: 1.5ml/min

Detector: UV at 238nm

Run time: 10/15 minutes

Injection volume: 10µl (as per the USP) or 20µl (as per BP 2008)

Buffer solution: 3.9g of monobasic sodium phosphate was dissolved in 900ml of water. the pH was adjusted to 4.5, if necessary, with either 50% sodium hydroxide or 85% phosphoric acid, and diluted with water to 1000ml, and mixed (USP, 2007) OR as per the BP (2008), 5.1g of sodium dihydrogen orthophosphate was dissolved in 900ml of water, adjusted the pH to 4.5 with either orthophosphoric acid or 1M sodium hydroxide and sufficient water was added to produce 1000ml.

Sample diluting solution: 3.0ml of glacial acetic acid was added to 900ml of water. The pH was adjusted to 4.0 with 5N sodium hydroxide and diluted with water to 1000ml. 200ml of this solution was mixed with 800ml of acetonitrile for the preparation of sample diluting solution. This was used to prepare samples from simvastatin tablets and solid dispersions for the estimation of the simvastatin content.

The buffer solution and diluting solution were filtered through 0.45μm membrane filters (Polyamide) (Schleicher & Schuell microscience, Dassel, Germany).

Calibration curve of simvastatin

Simvastatin (HPLC grade) stock solution of 0.25mg/ml was prepared in triplicate. The stock solution was further diluted using the sample diluting solution by serial dilution method to obtain samples within the concentration range of 0.0156 - 0.25mg/ml. The response (peak area) for each concentration was determined using the HPLC method described above and a calibration curve for simvastatin was plotted and fitted by linear regression analysis. The correlation coefficient was found to be r^2= 0.9996 indicating an excellent linearity.

The representative equation of the standard calibration curve of simvastatin obtained was:

$$Y = 2.0514X + 0.0046 \ (r^2 = 0.9996) \qquad \text{(eq 2.16)}$$

Where, Y = absorbance and X = concentration (mg/ml)

2.1.5.10.2. Verification of the assay sample preparation

The suitability of the HPLC method was verified by analysing simvastatin reference standard. The simvastatin API was standardised as a secondary in-house standard. Physical mix of known amounts of simvastatin API with various formulation excipients was analysed.

The simvastatin reference standard (SIM-RS), HPLC grade, bought from Sigma-Aldrich (Ireland), was suitably diluted by using a diluting solution to obtain a concentration of 0.125mg/ml. Similarly, simvastatin raw material (SIM-RAW) obtained from Leochem, (China) was used to prepare a solution of almost similar concentration. Both, solutions of SIM-RS and SIM-RAW were filtered through a 0.45µm hydrophilic PVDF filter before undertaking HPLC analysis. HPLC traces of SIM-RS and SIM-RAW were found to be nearly similar, showing retention times of 10.20 minutes and 10.26 minutes, respectively as outlined in Figure 2.4.

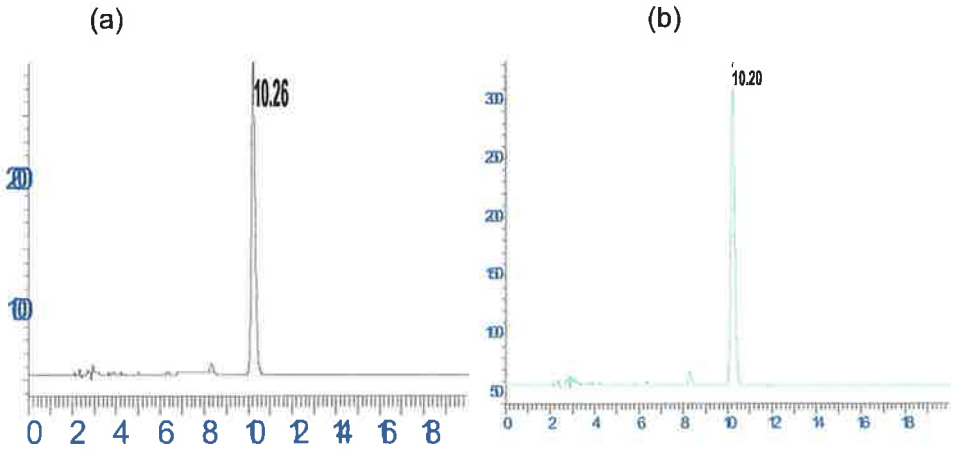


Figure 2.4: A representative HPLC chromatogram showing simvastatin peak for (a) Simvastatin RS (0.125 mg/ml) and (b) Simvastatin API (0.1 mg/ml)

A physical mix (PM) of simvastatin with the most frequently used tableting excipients/blends containing 10% w/w of simvastatin was prepared. The PMs studied were (1) Simvastatin (10%w/w) + Mannitol 200 (90%w/w) (PMI) - (0.1

mg/ml simvastatin) and (2) Simvastatin (10%w/w) + Mannitol 200 (84.5%w/w) + Kollidon CL-SF (5%w/w) + MgS (0.5 %) (PMII) - 0.2mg/ml designated as. Corresponding solutions were prepared using the diluting solution as described above for simvastatin tablets, to generate a solution with resultant concentration in the range 0.1-0.2 mg/ml and subjected to HPLC analysis. The HPLC chromatogram of both the physical mixtures, PMI (10.22 minutes) and PMII (10.22 minutes), containing simvastatin were found to show a marginal shift in retention time (10.22 minutes) compared to SIM-RS (10.20 minutes) and SIM-RAW (10.26 minutes) (Figure 2.5). No additional peaks were observed.

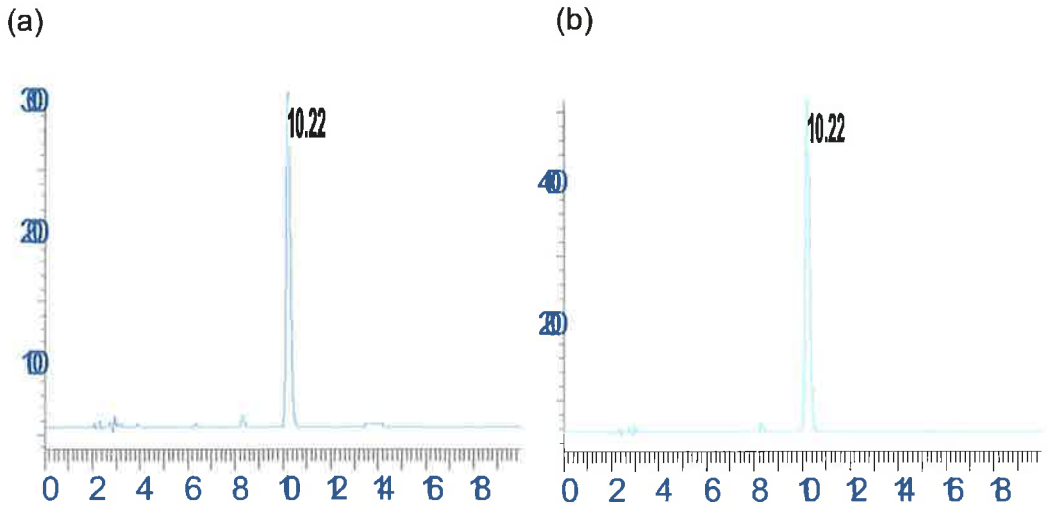


Figure 2.5: A representative HPLC chromatogram showing simvastatin peak for physical mix (PM) of simvastatin with tableting excipients for (a) PM I (simvastatin (10%w/w) + Mannitol 200 (90%w/w)) (0.1mg/ml) and (b) PM II (simvastatin (10%w/w) + Mannitol 200 (84.5%w/w) + Kollidon CL-SF (5%w/w) + MgS (0.5 %)) (0.2mg/ml).

Further, intra-assay precision was determined by analysing a 0.25mg/ml of simvastatin RS injected five times all on the same day. Precision of the assay was assessed by similarity of peak areas and retention times between each

injection, thus giving an indication of the repeatability of the assay. Results outlined in Table 2.6 indicate that the sample injections were found to be reproducible.

Table 2.6: Intra-assay precision of 0.25mg/ml standard using HPLC assay for simvastatin detection (n=5)

Retention time (minutes)	Peak area x 10^6	Concentration (mg)	Accuracy (%)
10.21 ± 0.00	6.4066 ± 0.073	0.25622 ± 0.00298	102.49

Subsequently, the HPLC flow rate was increased from 1.0ml/minute to 1.5ml/minute to decrease the analysis time. Solutions of both, SIM-RS and SIM-RAW were prepared as per the method outlined above and set for HPLC analysis. The resultant chromatogram showed a peak corresponding to simvastatin at a relatively lower retention time of 6.57 minutes and 6.55 minutes, respectively (Figure 2.6), compared to 10.20 minutes and 10.26 minutes at the lower flow rate of 1.0ml/minute (Figure 2.4). As a result, the run time of each sample was decreased from 20 minutes to 10 minutes.

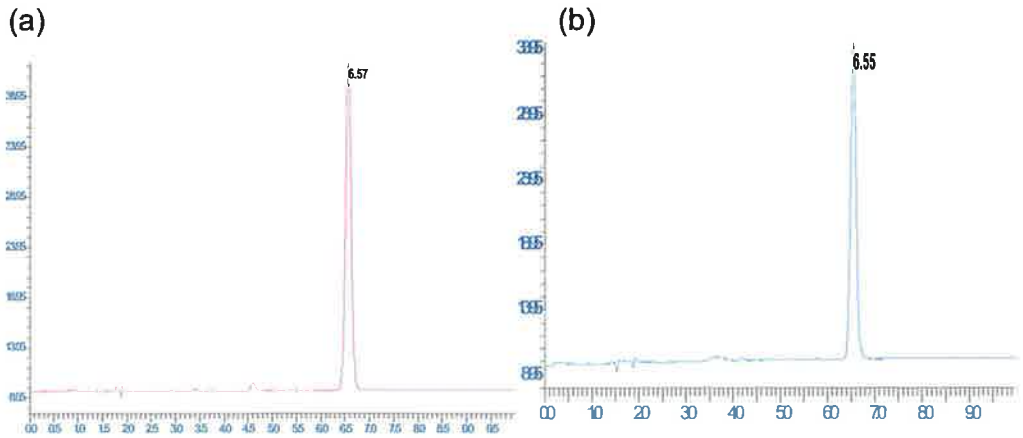


Figure 2.6: A representative HPLC chromatogram showing simvastatin peak for (a) SIM RS (0.125mg/ml) and (b) SIM API (0.1 mg/ml)

The simvastatin HPLC assay method was verified using simvastatin innovator tablets (Zocor®) and in-house produced FDDTs. The samples were prepared as per the procedure outlined in the methods section to obtain a solution with a concentration of approximately 0.1mg/ml of simvastatin. The tablets were assayed individually. The chromatograms revealed a retention time of 6.56 minutes for Zocor® tablets, which was found to be similar to the retention time of 6.63 minutes for the RCSI formulated FDDT (Figure 2.7).

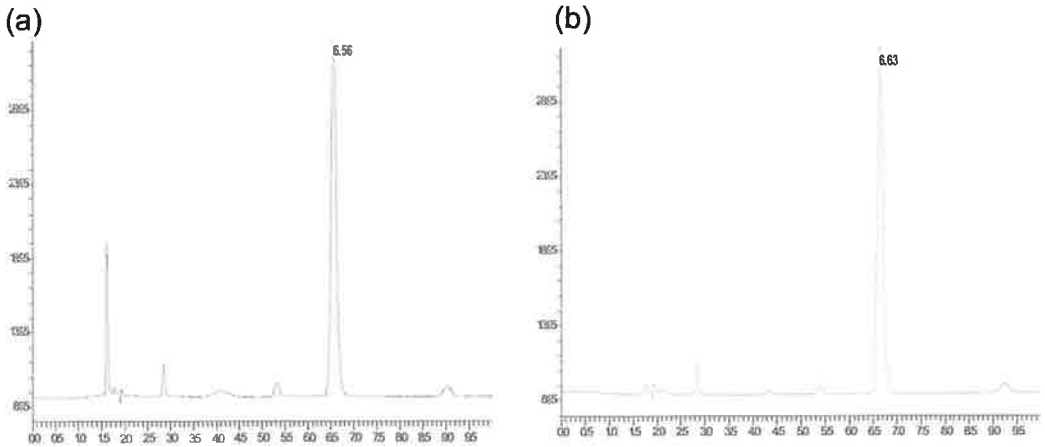


Figure 2.7: A representative HPLC chromatogram showing simvastatin peak from (a) Zocor® tablets 10mg (0.1mg/ml), Merck and (b) FDDT, 10mg (0.1mg/ml), RCSI (Batch. no. B044).

Sample preparation for simvastatin standard

An accurately weighed quantity of USP simvastatin RS was dissolved in diluting solution, and diluted quantitatively and stepwise if necessary, with diluting solution to obtain a solution having a known concentration of about 0.1mg/ml.

Sample preparation for assay of simvastatin tablets (as per USP and BP):

A quantity of whole tablets containing 0.16g of simvastatin was withdrawn randomly and transferred to a 250ml volumetric flask. A small volume of water

(not more than 10ml) was added and swirled to disintegrate the tablets. The sample was diluted to volume using the sample diluting solution, sonicated for 15 minutes, and allowed to cool to room temperature. If necessary, the final volume was adjusted with sample diluting solution. A portion of the mixture was centrifuged and three portions of the clear supernatant were diluted with diluting solution to obtain a solution having a concentration of about 0.1mg of simvastatin per ml. The samples were analysed for simvastatin content using the HPLC method described above. The amount of simvastatin in each formulation was calculated by substituting the peak area derived in the following equation 2.17. The resultant drug content was reported in percentage.

$$\frac{amt\ of\ sim\ in\ assay\ prep\ (mg/ml)}{amt\ of\ sim\ in\ s\tan dard\ prep\ (mg/ml)} = \frac{peak\ area\ of\ assay\ prep}{peak\ area\ of\ s\tan dard\ prep} \qquad \text{(eq 2.17)}$$

Assay of simvastatin from spray dried solid dispersions of simvastatin

The simvastatin content in the solid dispersions was also determined using the HPLC analysis. An appropriate quantity of the simvastatin solid dispersion equivalent to 1-2mg of simvastatin was accurately weighed and then suitably diluted using the HPLC sample diluting solution to obtain a concentration of about 0.1 - 0.2mg/ml of simvastatin. The solution was filtered through 0.45µm hydrophilic PVDF filter (Millipore Millex - HV) into HPLC vials (Apex scientific, Ireland) and analysed for drug content using the HPLC method described above.

The assayed content of drug was calculated using the calibration equation 2.16.

2.1.5.11. Dissolution studies on simvastatin FDDTs

Dissolution tests were carried out on the simvastatin formulations to investigate amount of drug dissolved with respect to time. The dissolution

medium used was prepared as per the method outlined in the USP for simvastatin tablets, and is outlined below.

Dissolution medium: pH 7.0 buffer solution containing 0.5% sodium dodecyl sulfate in 0.01M sodium phosphate prepared by dissolving 30g of sodium dodecyl sulfate and 8.28g of monobasic sodium phosphate in 6000ml of water, and adjusted with 50% (w/v) sodium hydroxide to a pH of 7.0; 900ml volume used.

Apparatus 2: 50rpm

Time: 30 minutes

Tolerances: Not less than 75% of the labeled amount of $C_{25}H_{38}O_5$ dissolved in 30 minutes.

Dissolution studies were carried out at a small scale on the simvastatin API. To avoid any floating of the drug particles on the surface of the dissolution medium, 5mg and 8mg of simvastatin was filled into a size "2" hard gelatin capsule. The dissolution test was carried out in 100ml of the dissolution medium using a shaking water bath at 100rpm and samples were withdrawn at interval of multiple of 2 starting from 15 minutes till 2 hours. The withdrawn samples were filtered using 0.45um filter and analyzed for total amount of drug dissolved using a USP based HPLC method and calibration curve as described above.

Dissolution studies on simvastatin FDDTs and commercial simvastatin tablets, Zocor® were carried out. These were analysed using the method outlined in the USP and described above on n=6 tablets. Samples were withdrawn at 30 minutes filtered using 0.45um filter and assayed for drug content using the HPLC method of analysis. At each time point the withdrawn volumes were replaced by equal amounts of fresh medium. A correction was made to take into account the cumulative sample volumes that had been withdrawn when determining the total amount dissolved as a function of time.

Dissolution studies in certain cases were carried out using the method as outlined in the BP 2008 described below.

The dissolution test for simvastatin (FDDT or Zocor®) according to BP 2008 was carried out using Apparatus 2. The medium used was 900ml of 0.01M sodium dihydrogen orthophosphate containing 0.5% w/v of sodium dodecyl sulphate and adjusted to pH 7.0 with 1M sodium hydroxide. The paddle was set to rotate at 50rpm. After 30 minutes, a sample of 20ml of the medium was withdrawn, filtered using 0.45um filter and 10ml of the filtrate was transferred into a centrifuge tube containing 0.1g pre-washed manganese (IV) oxide. The tube was shaken for 30 minutes, or until the manganese (IV) oxide was completely dispersed, centrifuged. The clear supernatent liquid was suitably diluted with dissolution medium if necessary and absorbance was measured at maximum wavelength of 247nm and at the minimum wavelength of 257nm, using the dissolution medium that has been similarly treated with pre-washed manganese (IV) oxide in the reference cell. At the same time the absorbance of a suitable solution of simvastatin BP was measured at 247nm and at 257nm. It was prepared by dissolving simvastatin BP in the dissolution medium and treating with pre-washed manganese (IV) oxide as described above.

The total content of simvastatin, $C_{25}H_{38}O_5$, in the medium was calculated using the differences in absorbance at 247nm and at 257nm and using the declared content of $C_{25}H_{38}O_5$ in simvastatin BPCRS.
The samples were withdrawn at various time points i.e. 5, 10, 20, 30 and 60 minutes and the amount of drug released was determined using the UV method as per the procedure outlined above. The cumulative amount of drug released at each time point was calculated and plotted as percent drug released against time (minutes).

2.1.6. Data analysis

In this thesis the results obtained are expressed as a mean ± standard deviation calculated using Microsoft Excel (Redmond, WA, USA) software. Statistical analysis was performed using SPSS version 15.0 for windows

(SPSS, Inc, Chicago, IL, USA). For comparison between average values of one batch with several other batches, one sample t test was utilised. Whereas, where comparison between two groups were required, an independent sample t test was used. In addition, to test the difference between three or more groups, one-way ANOVA was used. In the event where the differences in the mean values were statistically significant, post hoc analysis were done using Tukey, where variances were equal and Tamhanes T2, where variances were not found to be equal. A p value of less than 0.05 was considered as statistically significant.

CHAPTER 3

Investigation of Formulation and Process Parameters on the Characteristics of Fast Disintegrating Fast Dissolving tablets prepared by Direct Compression

3.0 Introduction

The aim of this study was to investigate the effect of formulation composition and process variables on the characteristics of FDDTs prepared by direct compression. In chapter 1, a review of the techniques utilised for the preparation of FDDT showed that freeze drying or lyophilisation and tablet moulding tend to produce tablets with low mechanical strength, requiring specialized packaging. The conventional techniques of granulation tend to produce tablets which are more robust however they are associated with longer disintegration times. Although FDDTs formulated by direct compression have rapid disintegration, their mechanical strength was low. Attempts to enhance mechanical strength using a number of post compaction treatments were investigated. These included subjecting the FDDTs to storage or curing under specific conditions of temperature and humidity, adding additional steps or complexity to the overall process.

In this chapter, we investigated the combined effects of formulation and process variables on the properties of FDDTs formulated by direct compression. The objective was to design formulation and process parameters which will result in FDDTs with enhanced mechanical strength, a rapid disintegration and good palatability while using a process which is easily scalable and commercially feasible.

A range of direct compressible fillers in combination with one or more disintegrants or superdisintegrants were used to formulate placebo FDDTs. The influence of various process variables such as compression force, tablet shape and tablet dimension on the final tablet characteristics were also studied. A superdisintegrant is an excipient which causes rapid disintegration of tablets by rapid swelling/wicking/dispersing mechanism.

The sugar based directly compressible (DC) fillers; Mannitol, Sorbitol, Ludipress® (ludipress) which is a lactose based co-processed DC filler and

the cellulose based DC excipient, Prosolv® HD90 (Prosolv), a high density silicified microcrystalline cellulose were used to formulate FDDTs. The composition of the various fillers used is listed in Table 3.1.

Co-processed excipients are defined as a combination of two or more than two compendial excipients or non-compendial excipients by techniques such as a spray drying process, designed to physically modify their properties in a manner not achievable by simple physical mixing.

Table 3.1: Composition of various fillers used in the formulations presented in this chapter

Filler	Composition
Mannogem (Mannogem™ EZ)	Spray dried mannitol (manufactured by: SPI Pharma)
Mannitol 200 (Parteck®M200)	Spray dried mannitol (manufactured by Merck)
Mannitol 300 (Parteck®M300)	Spray dried mannitol (manufactured by Merck)
Sorbitol (Parteck®SI400)	Sorbitol (manufactured by Merck)
Ludipress (Ludipress®)	Lactose monohydrate + Kollidon® 30 (binder) + Kollidon® CL (disintegrant) (manufactured by BASF)
Prosolv (Prosolv® HD90)	High density silicified microcrystalline cellulose + colloidal silicon dioxide (manufactured by JRS Pharma)

For fast disintegrating tablets prepared by compression, the choice of disintegrant plays an important role in governing the disintegration time of the tablets (Dobetti, 2000). Various types of disintegrants/superdisintegrants differing in aqueous solubility and disintegration mechanism were studied.

The disintegrants used (Table 3.2) include a superabsorbent polymer, potassium polyacrylate, luquasorb (Luquasorb® 1280) which is supposed to cause disintegration of tablets by a swelling action. Two amorphous disintegrants, cross-linked sodium carboxymethyl starch, also called sodium starch glycollate (Explotab®; SSG) and cross-linked polyvinylpyrrolidone (crospovidone), (Kollidon® CLSF; K-CLSF) were evaluated. The SSG disintegrates the tablet predominantly by a swelling action whereas the K-CLSF absorbs water into the tablet by a wicking/capillary action. The naturally occurring silica based crystalline dispersible agent, calcium silicate (RxCIPIENTS® FM1000; CaS) and two water-soluble osmotic agents, citric acid anhydrous and sodium citrate anhydrous were also investigated as potential disintegrants.

Table 3.2: Characteristics of various disintegrants used in the formulations presented in this chapter

Disintegrants	Aqueous solubility	Mechanism of disintegration
Luquasorb® 1280 (luquasorb)	Insoluble	Extensive swelling
Explotab® (SSG)	Insoluble	Rapid and extensive swelling with minimal gelling
Kollidon® CLSF K-CLSF	Insoluble	Wicking and little swelling
Calcium Silicate (RxCIPIENTS® FM100); CaS	Insoluble	Dispersing agent by wicking action
Citric acid	Soluble (59.2% (20°C))	Osmotic agent
Sodium citrate	Soluble (72% (RT))	Osmotic agent

Conventionally, magnesium stearate (octadecanoic acid, magnesium salt), a hydrophobic lubricant, is used to facilitate efficient tableting of the formulation and ejection of the formed tablets. It has been reported that hydrophobic excipients can retard the disintegration time of FDTs (Yang et al., 2004). As

part of this study, various hydrophilic lubricants were added to the tablet blend and their effect on the tableting process and characteristics of the FDDTs formulated was examined. The four hydrophilic lubricants used two included polyethylene glycols differing in molecular weight (MW) i.e. Pluriol® E2000 (MW 2000) and Pluriol® E6000 (MW 6000) and polyethylene-polypropylene glycol - a difunctional block co-polymer and non-ionic surfactant of two molecular weights; Lutrol/Pluronic® F68 (Poloxamer 188, MW 8400) and Lutrol/Pluronic® F127 (Poloxamer 407, MW 12600).

To improve palatability and taste of the FDDTs, the influence of adding a range of flavouring agents on the characteristics of tablets was evaluated.

The process variables investigated included increasing compression force, varying tablet diameter, shape and tablet weight. Furthermore, the influence of increasing tablet turret speeds on selected formulations and the stability profiles of these formulations was evaluated.

3.1. Preformulation characteristics of the materials utilised in the production of FDDTs

The particle size analysis and flow properties of various fillers selected for the present study were measured and are given in Table 3.3. Two types of mannitol DC were evaluated; Mannogem (Mannogem^{TM} EZ) and Parteck® M, manufactured by different manufacturers. Mannogem (Mannogem^{TM} EZ) is the spray dried crystalline rounded shape mannitol manufactured by SPI Pharma with a median particle size 49.39μm (Table 3.3). As expected from its small particle size, Mannogem showed a Carr's index value of 20.91, reflective of "fair" flow property.

The spray dried mannitol manufactured by Merck KGaA is produced by a spray drying process causing the mannitol to crystallize in a needle-like microstructure. Two grades differing in median particle size; Mannitol 200

(Parteck® M200; M200) and Mannitol 300 (Parteck® M300; M300) was used. The median particle size measured for M200 and M300 was 94.52 and 193.42μm, respectively and showed excellent rheological property with Carr's index value of 10.47 and 7.44, respectively.

Sorbitol (Parteck® SI400) comprises of randomly oriented interwoven filamentary crystals. Sorbitol had the highest median particle size of 315.16μm and showed excellent rheological property as shown by its Carr's value of 5.93.

Ludipress (Ludipress®), a co-processed lactose based DC excipient comprises of lactose monohydrate at 93.0%w/w, Kollidon® 30 and Kollidon® CL at 3.5%w/w each, while, Prosolv® (Prosolv® HD90), a co-processed cellulose based DC excipient consists of 98%w/w of microcrystalline cellulose and 2%w/w of colloidal silicon dioxide (SiO_2). These showed a median particle size of 152.88μm and 127.12μm, respectively. Both exhibited good rheological properties as expected from their particle size.

Table 3.3: Particle size and flow properties of various fillers used in the formulations presented in this chapter (mean ± standard deviation)

Filler	D10% (μm)	D50% (μm)	D90% (μm)	SPAN	Carrs index*	Flow properties
Mannogem (Mannogem™ EZ)	6.27 ± 0.11	49.39 ± 1.24	121.34 ± 1.60	2.33 ± 0.04	20.91	Fair
Mannitol 200 (Parteck®M200)	19.90 ± 0.27	94.52 ± 1.01	301.83 ± 5.89	2.98 ± 0.07	10.42	Excellent
Mannitol 300 (Parteck®M300)	41.85 ± 3.30	193.42 ± 12.59	401.73 ± 23.62	1.86 ± 0.02	7.44	Excellent
Sorbitol (Parteck®SI400)	132.64 ± 5.76	315.16 ± 14.45	575.50 ± 20.06	1.41 ± 0.01	5.93	Excellent
Ludipress (Ludipress®)	41.96 ± 1.60	152.88 ±7.38	335.89 ± 9.84	1.92 ± 0.05	13.34	Good
Prosolv (Prosolv® HD90)	44.60 ± 2.46	127.12 ± 1.87	246.40 ± 4.29	1.59 ± 0.05	13.78	Good

* average of bulk and tapped density was used to calculate Carrs index

3.2. Influence of formulation variables on the characteristics of the FDDTs

3.2.1. Influence of the type of DC fillers

A range of DC fillers in combination with K-CLSF as superdisintegrant were compressed at a compressional force of 10kN using 13mm round FBE toolings at tableting speed of 7rpm and target tablet weight of 300mg. Magnesium stearate was used as a lubricant. The tablets obtained were characterised for their weight variation, mechanical properties and disintegration times. All batches formulated showed excellent weight uniformity, with variability of less than 1.45% (Table 3.4). The use of M200 showed the least weight variability (299.31 ± 0.86mg), while the use of Mannogem showed the highest weight variability (302.37 ± 4.38mg), probably related to the higher Carr's index and hence lower flowability of the Mannogem blend (Table 3.3).

Table 3.4: Influence of type of filler on the characteristics of 13mm round flat faced bevelled edge (FBE) tablets containing Kollidon CLSF (mean ± standard deviation)

Batch	Filler	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
B086	Mannogem	302.37 ± 4.38	13.19 ± 1.2	0.0260	failed[6]	5.67 ± 2.31	21.70
B079	Mannitol 200	299.31 ± 0.86	30.71 ± 1.16	0.0604	0.00	16.0 ± 1.00	24.97
B084	Mannitol 300	310.58 ± 0.97	27.82 ± 0.21	0.0542	failed[7]	9.67 ± 0.58	26.68
B085	Ludipress	307.83 ± 1.05	15.28 ± 0.8	0.0302	failed[7]	42.0 ± 2.65	20.55
B112	Prosolv	295.97 ± 2.68	96.98 ± 2.91	0.1958	0.00	11.0 ± 5.57	20.02

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6]1 tablets broke, [7]2 tablets broke - during the friability test

The low level of tablet weight variability can be associated with the fair to excellent rheological properties of the pre-processed fillers giving a uniform and consistent die fill during tableting.
The thickness of the tablets was found to be in the range of 1.99 - 2.27mm. The lowest thickness observed was for the Prosolv® tablets at 1.99mm and the highest for the Mannitol 300 at 2.27mm. The porosity of the tablets were highest for Mannitol 300 and lowest for the Prosolv® tablets.

Among the three grades of mannitol employed; Mannogem® and M300 formed tablets with lowest hardness and tensile strength. These tablets were found to be friable, whereas M200 produced tablets with good tensile strength (Figure 3.1). This behaviour can probably be attributed to superior compression properties of M200 filler. In spite of the fact that Ludipress® is a lactose based co-processed excipient with a binder Kollidon® 30 at 3.5%w/w, it formed tablets with low tensile strength and were found to be friable. On the contrary, the Prosolv® based tablets were characterised by significantly high (ANOVA; $p < 0.0001$) hardness and tensile strength compared to all other DC fillers. Prosolv consists of microcrystalline cellulose which is utilised in tableting for its diluent, binding and disintegrant properties (Swarbrick and Boylan, 1991). This observation was consistent with earlier studies carried out on various grades of microcrystalline cellulose where it was found that high density silicified microcrystalline cellulose (Prosolv® HD) exhibited enhanced mechanical strength (Steele et al., 2004).

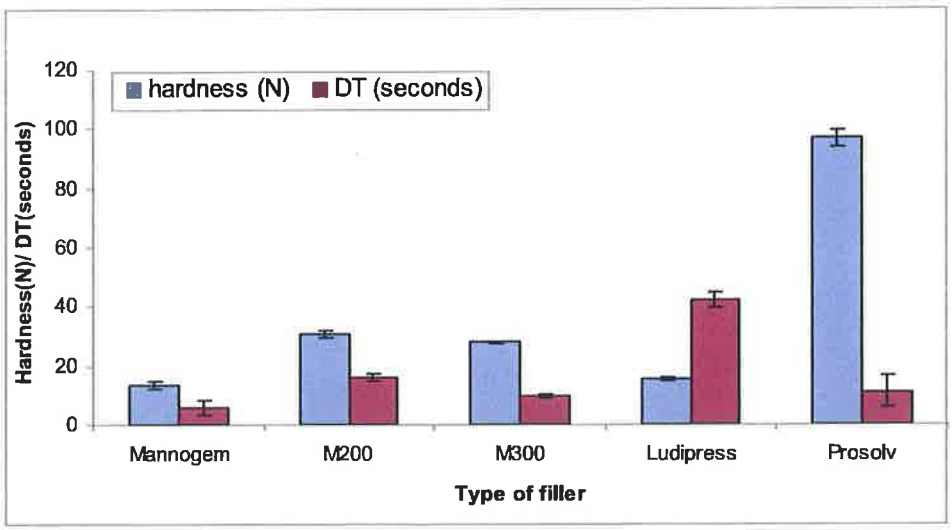


Figure 3.1: Influence of type of filler on the hardness and disintegration time of 13mm FBE tablets prepared using K-CLSF as a disintegrant

The mannitol based DC fillers; Mannogem®, M200, and M300 and the cellulose based filler, Prosolv® possessed a comparable DT ($p > 0.05$), in the range 5.67 - 16 seconds. Mannogem and M300 showed the lowest DT values probably related to their low hardness or high porosity, while M200 correspondingly had a higher disintegration time of 16 seconds. Despite its much higher hardness value, Prosolv® dispersed easily when in contact with water giving a low DT of 11 seconds. This was probably due to the presence of colloidal silicon dioxide that helps to impart good disintegrant properties to the compact (Tobyn et al., 1998). The DT of the Ludipress® tablets was the highest at 42 seconds despite it being a co-processed excipient containing a disintegrant Kollidon® CL at 3.5%w/w and its low hardness value.

The two sugar alcohol fillers, M200, sorbitol and a sugar alsohol based co-processed filler, Ludipress® was also tableted using a combination of the superdisintegrant, SSG and the dispersant, calcium silicate (CaS). Magnesium stearate was added as a lubricant. The tablets were compressed at a target tablet weight of 550mg using a compression force of 10kN and 15mm round FBE toolings.

The characterisation data in Table 3.5 show good weight uniformity with a standard deviation of ±0.33% of the average weight, irrespective of the filler used. The thickness of the tablets was found to be in the range 2.63 to 2.78mm.

Among the three fillers, the hardness of sorbitol tablets was significantly higher (ANOVA; $p < 0.0001$). This was attributed to its good binding properties, as sorbitol is used as a diluent-binder (Cargill.com). As was found previously (Table 3.4), Ludipress® based tablets showed the lowest hardness at 11.15N and failed the test of friability. On the other hand, mannitol based tablets possessed considerably better mechanical properties and showed no weight loss during friability testing

Table 3.5: Influence of type of filler in combination with superdisintegrant, SSG and dispersant, CaS on the characteristics of 15mm round FBE tablets

Batch	Filler	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
B014	M200	551.06 ± 0.87	37.05 ± 1.41	0.0425	0	37.33± 3.79	30.04
B015	Sorbitol	552.94 ± 1.82	64.00 ±3.10	0.0735	0.15	151.6± 27.21	27.38
B012	Ludipress	575.54 ± 0.28	11.15 ± 0.64	0.0124	Failed	71.67± 3.06	24.75

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time,

Among the formulations examined, M200 based FDTs were associated with the lowest DT of 37.33 seconds whereas, despite a ten-fold higher aqueous solubility of sorbitol compared to mannitol (Zabozlaev et al., 2007), sorbitol based tablets showed the highest disintegration of 151.6±27.21 seconds, as expected from their high hardness at 64N. Despite the fact that Ludipress® is co-processed filler containing a disintegrant and that its hardness was lowest at 11.15N, its DT was high at 71.67 seconds (Figure 3.2). The DT of the

tablets was related to the porosity of the tablets, M200 had the highest porosity of 30.04% and correspondingly lowest DT of 37.33 seconds, while the porosity of sorbitol and ludipress were lower at 27.38% and 24.75%, respectively. High porosity of tablets is associated with easy uptake and penetration of water into the tablet matrix facilitating the hydration of the superdisintegrant, and quick disintegration of the tablets.

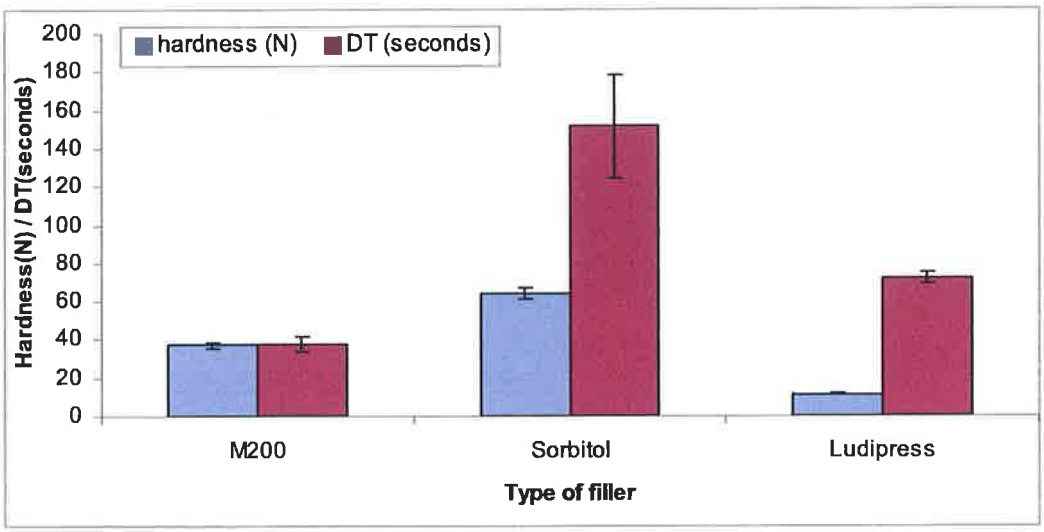


Figure 3.2: Influence of type of filler on the hardness and disintegration time of 15mm FBE tablets comprising a combination of CaS and SSG as disintegrant

In conclusion, Mannitol 200 and Prosolv® were preferred fillers due to their high mechanical strength and lower disintegration time.

3.2.2. Investigation of various types of disintegrants

Based on the above data, Mannitol 200 was selected to study the effect of various superdisintegrants, because mannitol is water soluble therefore would give good palatability compared to Prosolv® which is water insoluble. The disintegrants differing in their disintegration mechanism on the disintegration time and mechanical properties of FDDTs was evaluated. Magnesium stearate was used as lubricant and compressed at a compressional force of 10kN using 15mm round FBE toolings. The level of disintegrant used ranged from 2%w/w (for Luquasorb®) to 18%w/w (for calcium silicate) depending on

the manufacturer's recommended level. Characteristics of the FDDTs formulated show that all tablets had a low weight variation (variability ±1.35%) irrespective of the type of disintegrant incorporated (Table 3.6).

The hardness and tensile strength was found to be a function of the type of disintegrant used. In addition, various tablets were conferred with different disintegration times depending on the type of superdisintegrant used. Tablets consisting of Luquasorb®, SSG and K-CLSF as superdisintegrants were mechanically strong with a hardness of 36.49N, 49.47N and 45.73N, respectively. The tablets formed had low friability of <1% (Table 3.6 and Figure 3.3). The thickness of the tablet was found to be in the range 2.55 - 2.91mm.

Table 3.6: Characteristics of 15mm FBE Mannitol 200 tablets formulated using different disintegrants, compressed at 10kN

Batch no	Disintegrant (%w/w)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
B20	Luquasorb® (2%w/w)	497.58 ± 2.74	36.49 ± 2.56	0.0422	0.60	12.20 ± 1.48	23.53
B32	SSG (10%w/w)	549.12 ± 7.39	49.47 ± 2.05	0.0555	0.91	36.67 ± 4.93	32.11
B46	K-CLSF (5%w/w)	487.40 ± 0.35	45.73 ± 2.21	0.0521	0.81	12.33 ± 0.58	29.54
B27	CaS (18%w/w)	511.76 ± 5.37	33.64 ± 6.05	0.0421	failed[6]	11.00 ± 4.18	34.95
B48	Citric acid (10%w/w)	521.60 ± 4.66	55.46 ± 3.04	0.0630	0.61	14.80 ± 1.79	26.45
B49	Na citrate (10%w/w)	510.91 ± 6.73	47.13 ± 3.03	0.0538	0.61	08.20 ± 0.84	24.26

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6]9 tablets broke

The Luquasorb® based tablets disintegrated in 12.20 seconds similar to the DT of FDDTs containing crospovidone, K-CLSF. The swelling capacity of luquasorb was reported to be 58.92% (BASF), which contributes to the low disintegration time. The DT of SSG containing FDDTs was found to be significantly longer at 36.67 seconds than FDDTs consisting of K-CLSF or luquasorb or other disintegrants, ($p < 0.0001$) (Table 3.6 and Figure 3.3), despite the higher porosity value of 32.11% for tablets containing SSG. This can be attributed to a difference in disintegration mechanism. SSG causes a tablet to disintegrate by extensive swelling which is also accompanied with gelling, whereas K-CLSF acts by water wicking and swelling. Zhao and Augsburger, (2006) reported the swelling capacity of the superdisintegrant in terms of an increase in diameter as 251% for SSG and 29% for crospovidone (K-CLSF). Since the swelling is accompanied with the gelling in case of SSG, it could possibly occlude the pores preventing further penetration of water into the tablet matrix hence leading to the delay in disintegration of tablets.

Wicking may be defined as the phenomenon of drawing water into the tablet by providing pathways for the penetration of fluid into tablets through capillary action resulting in rupture of the interparticulate bonds causing the tablet to break apart. In previous studies, the capillary activity of crospovidone for water was reported to be majorly responsible for its tablet disintegration property, probably attributed to its porous particle morphology (Kornblum and Stoopak, 2006).

The trend of DT observed in this study was similar to that reported by Fini et al (2008). These authors reported a DT of > 1 minute for FDDTs containing mannitol with SSG, while a DT of 32 seconds was obtained for the corresponding tablets containing Kollidon® CL.

The use of calcium silicate alone, as a dispersing agent, led to the formation of tablets with the lowest hardness and tensile strength compared to other tablets (Figure 3.3), and hence failed friability testing. This was attributed to the low binding of the tablet matrix due to the presence of calcium silicate. The tablets formed using calcium silicate had the highest porosity at 34.95%

probably accounting for its fast disintegration in 11 seconds. The high porosity of these tablets could be due to the porous nature of calcium silicate, which were retained during compression into tablets (Kanaya, 1996).

The use of the water-soluble osmotic agents; citric acid and sodium citrate produced hard tablets, with low friability of less than 1% and both osmotic agents produced tablets with fast DT of less than 15 seconds. This fast disintegration is related to their high water solubility.

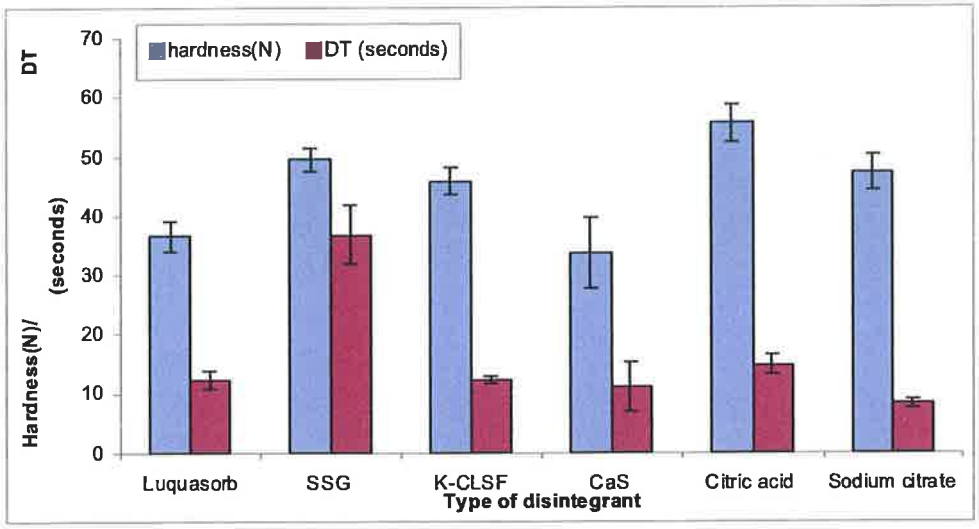


Figure 3.3: Influence of various disintegrants on the hardness and disintegration time of 15mm FBE tablets prepared using M200

The above study was repeated (using Mannitol 200), except 13mm toolings were used rather than 15mm. In addition, Prosolv® as filler was investigated to evaluate the various disintegrants with different disintegrant mechanism. The three superdisintegrants; Luquasorb®, SSG, K-CLSF and a combination of SSG and CaS were evaluated. Magnesium stearate was included in the blend as a lubricant. The tablet blend was compressed at 10kN to generate 300mg tablets.

The FDDTs formulated showed a low weight variation (maximum standard deviation of ±0.91%), irrespective of the filler or disintegrant used (Table 3.7).

Table 3.7: Effect of superdisintegrants on the characteristics of tablets prepared using M200 and Prosolv® 13mm FBE FDDTs

Disintegrant	Filler	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
Luquasorb (B115)	Prosolv HD90	301.20 ± 1.95	119.6± 6.98	0.2398	0.10	47.67 ± 3.06	21.56
Luquasorb (B060)	M200	299.55 ± 4.28	21.13 ± 2.48	0.0414	0.66	02.33 ± 0.58	27.50
SSG (B113)	Prosolv HD90	299.18 ± 0.59	141.1± 7.14	0.2824	0.00	07.33 ± 0.58	25.48
SSG (B058)	M200	297.54 ± 2.71	28.89 ± 6.45	0.0452	0.00	19.27 ± 2.52	19.21
SSG+CaS B114	Prosolv HD 90	302.24 ± 0.20	76.91 ± 1.96	0.1549	0.00	05.33 ± 1.15	25.23
SSG+CaS B101	M200	296.36 ± 0.68	29.78 ± 0.81	0.0512	0.36	17.69 ± 2.08	20.51
K-CLSF (B112)	Prosolv HD90	295.97 ± 2.68	96.98 ± 2.91	0.1958	0.00	11.00 ± 5.57	20.02
K-CLSF (B057)	M200	304.77 ± 0.64	30.74 ± 1.08	0.0601	0.33	15.67 ± 1.53	25.84

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time

The thickness of the Prosolv® based tablets was found to be lower, in the range of 1.99 - 2.04mm while the thickness of M200 based tablets was found to be in the range of 2.08 - 2.24mm.

The use of Prosolv® generated tablets with higher hardness and tensile strength at ~3-4 fold higher, compared to tablets formulated with M200 as filler, irrespective of the disintegrant used (Table 3.7 & Figure 3.4). Prosolv based tablets disintegrated faster compared to the corresponding mannitol based tablets. The DT of Prosolv® based tablets was in the range of 5 to 11 seconds, compared to the disintegration of 15 to 20 seconds for M200 based tablets (Table 3.7, Figure 3.4). An exception was found in the case of

Luquasorb® based tablets, where the DT of the Prosolv® tablets was significantly higher than for corresponding M200 tablets ($p < 0.05$). The DT of the M200 tablets containing luquasorb was found to be low at 2.33 seconds. This is the fastest DT observed for a DC FDDT, which, in addition, passed the friability test. The disintegration time of the M200 tablets when K-CLSF was included was similar to the DT of the corresponding Prosolv® tablets. Addition of calcium silicate to SSG did not enhance the DT of either M200 or Prosolv® tablets although it resulted in a decrease in hardness of the prosolv FDDTs.

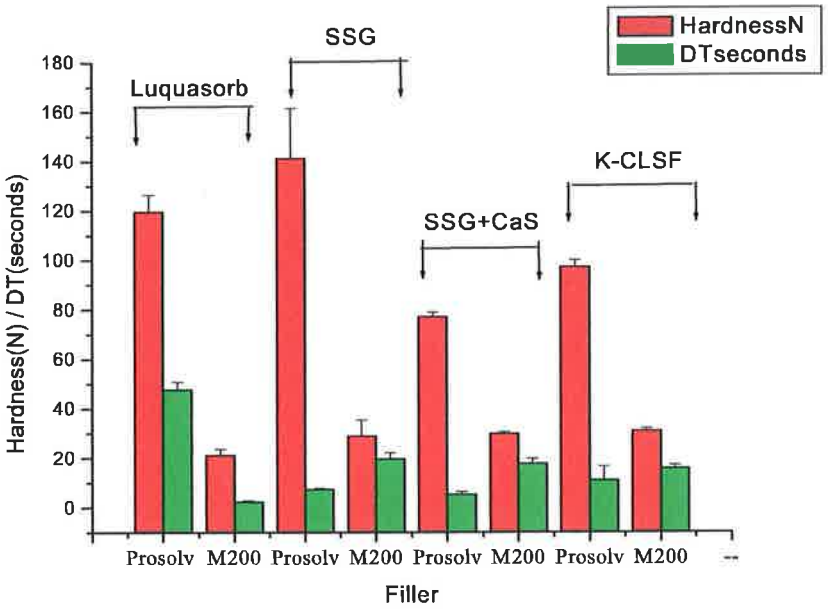


Figure 3.4: Comparison between the characteristics of tablets prepared using M200 and prosolv as fillers in combination with various superdisintegrants

3.2.3. Effect of type of lubricant

Lubricant is usually added to the tablet blend to facilitate tableting of the formulation and ejection of the formed tablets by reducing the friction between the powder bed and the die walls during compression and ejection. The type of lubricant used can have a profound influence on the powder properties,

such as its flow properties for ease of filling into die cavity, plasticity of powders which helps compact formation and the final tablet characteristics such as hardness, disintegration time and drug dissolution. Magnesium stearate (MgS) is the most commonly used lubricant in tableting. It is hydrophobic and hence can affect the wettability and disintegration time of tablets, particularly when the active is poorly water-soluble. In the case of FDDTs, addition of magnesium stearate as a lubricant may add to the disintegration time of the tablets which would not be desirable (Kuno et al., 2008; Late et al., 2009; Mužíková, 2007).

In this study, the use of a range of hydrophilic lubricants on the characteristic of FDDTs were evaluated and compared with tablets formulated using the hydrophobic lubricant, magnesium stearate. The four hydrophilic lubricants include two polyethylene glycol types differing in molecular weights i.e. Pluriol® E2000 (Molecular weight (MW) 2000) and Pluriol® E6000 (MW 6000) and polyethylene-polypropylene glycol, a difunctional block co-polymer and non-ionic surfactant of two molecular weights; Lutrol/Pluronic® F68 (Poloxamer 188, MW 8400) and Lutrol/Pluronic® F127 (Poloxamer 407, MW 12600). The lubricant was added at 0.5%w/w of the tablet blend. Tablets were also formulated at a lower level of magnesium stearate at 0.3%w/w. Mannitol 200 was used in combination with K-CLSF to produced tablets compressed at 10kN, using 10mm round FBE toolings.

Tablets of uniform weight with low weight variability of 0.99% were produced, regardless of the type of lubricant employed (Table 3.8). This implies that the blend has a good flowability probably due to the excellent flow properties of M200, independent of the type of lubricant employed.

Table 3.8: Influence of the type of lubricant on the characteristics of 10mm round FBE tablets compressed using M200 as a filler and K-CLSF as a superdisintegrant

Lubricant type	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
MgStearate (0.30%w/w)	204.20 ± 1.20	50.70 ± 3.27	0.1535	0.14	21.17 ± 4.96	18.72
MgStearate (0.50%w/w)	202.81 ± 2.01	54.30 ± 2.38	0.1644	0.13	23.33 ± 5.76	19.22
Pluriol®E2000 (0.50%w/w)	199.33 ± 1.89	49.22 ± 2.56	0.1495	0.23	19.83 ± 6.05	18.47
Pluriol®E6000 (0.50%w/w)	199.80 ± 1.27	50.67 ± 3.89	0.1541	0.09	27.17 ± 5.12	19.32
Lutrol®F68 (0.50%w/w)	196.51 ± 1.87	48.77 ± 2.12	0.1492	0.12	32.00 ± 6.10	17.66
Lutrol®F127 (0.50%w/w)	197.44 ± 1.57	48.12 ± 2.59	0.1472	0.18	25.83 ± 3.19	17.27

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time

Tablet thickness was found to be in the range 2.26 to 2.33mm. The hardness and the tensile strength of the tablets consisting of magnesium stearate at 0.3%w/w and 0.5%w/w was found to be similar to the tablets containing a hydrophilic lubricant at 0.5%w/w and was in the range of 48.12 - 54.30N (Figure 3.5). Irrespective of the type of lubricant, all the tablets exhibited a weight loss of less than 0.23% during the test of friability.

Of the hydrophilic lubricants, despite of the fact that Lutrol® F127 is less water-soluble than Lutrol® F68, the DT for the former was found to be lower at 25.83 seconds compared with Lutrol® F68 (DT=32 seconds). This can be due to the fact that Lutrol® F127 has a higher swelling capacity and also presents a higher water uptake compared to Lutrol® F68 (Jannin et al., 2006).

The DT of the tablets consisting only Pluriol® E2000 was lower at 19.83 seconds, than the DT tablets containing hydrophobic lubricant, MgS at 21.17 seconds and 23.33 seconds, at 0.3%w/w and 0.5%w/w, respectively. Overall, the average DT values observed for the other hydrophilic lubricants were higher than for FDDTs formulated with magnesium stearate.

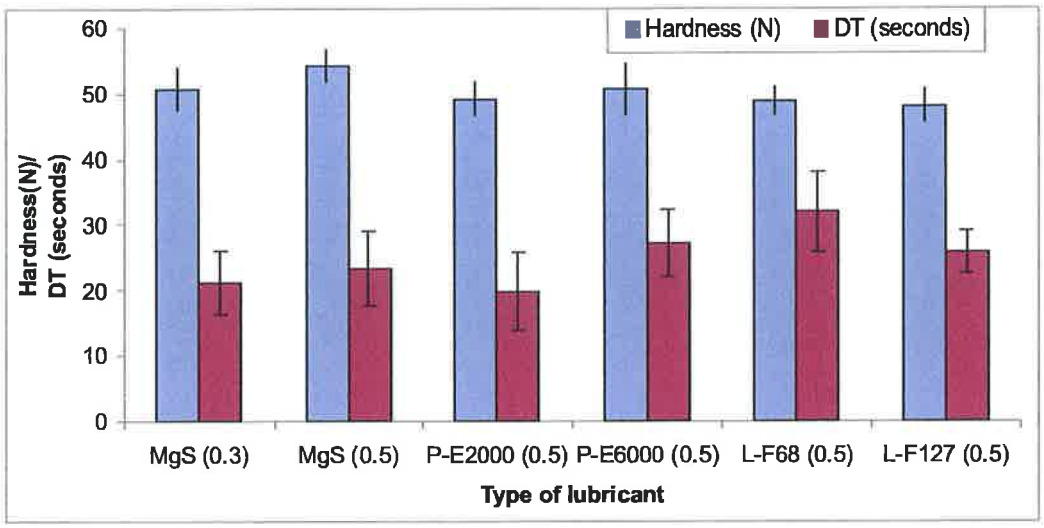


Figure 3.5: Influence of type of lubricants on the hardness and disintegration time of the 10mm FBE tablets containing M200 and K-CLSF

3.2.4. Inclusion of various types of flavours

Since an FDDT is designed to disintegrate in the patients mouth, the development of an optimum FDDT requires consideration of the taste and palatability. In addition most drugs have an unpleasant taste and therefore require taste masking. Taste masking and palatability enhancement strategies of oral formulations such as suspensions, solutions, chewable, fast dissolving and dispersible tablets have ranged from addition of sugars, sweeteners, flavours to microencapsulation of the active depending on its taste. Another factor is the general grittiness of formulations which leave an unpleasant mouthfeel. It is recognised that particles <125 μm give a smooth mouthfeel. While sugar based FDDT formulations generally have an acceptable taste

and pleasant mouthfeel, additional taste enhancement is generally required to mask the taste of the drug. The addition of a flavour or combination of flavours to the sugar alcohol based Mannitol FDDT formulation and its influence on the characteristics of the FDDTs manufactured was examined. The flavours examined were raspberry (F1), cherry black (F2), chocolate (F3), vanilla cream (F4) or a combination of chocolate and vanilla. The flavours were included at 0.8%w/w, which was maximum allowed concentration for oral drug delivery, as per the manufacturers recommendations, except for chocolate which was used at 2%w/w when in combination with other flavours and 4%w/w when on its own.

Tablets were compressed using M200 as filler, K-CLSF as a superdisintegrant and magnesium stearate as the lubricant. Tablets were compressed at 10kN using 15mm round FBE toolings. The tablets showed little or no change in the weight of the tablets irrespective of the flavours used (Table 3.9). Thickness of the tablets was found to be in the range 2.73 - 2.84mm.

Table 3.9: Influence of adding various flavours on the characteristics of tablets formulated using 15mm FBE tools

Batch no	Flavours (%)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
B46	No flavour	487.40 ± 0.35	45.73± 2.21	0.0521	0.81	12.33 ± 0.58	29.54
B58	F1 (0.6)	506.06 ± 3.98	31.57 ±10.18	0.0357	0.77	13.67 ± 2.52	28.81
B59	F2 (0.6)	503.49 ± 1.23	31.81± 1.32	0.0359	0.99	18.36 ± 0.58	29.94
B69	F3 (4)	510.62 ± 3.60	24.77± 2.19	0.0280	0.2	18.03 ± 2.52	28.63
B67	F4 (0.6)	510.3± 2.68	28.29± 2.06	0.0321	0.2	17.00 ± 1.00	27.17
B68	F3+F4 (0.6+2)	510.38 ± 3.45	27.45± 1.35	0.0310	0.98	18.33 ± 0.58	29.52

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, F1 - Raspberry, F2 - Cherry black, F3 - Chocolate, F4 - Vanilla cream

Addition of various types of flavours caused a decrease in hardness and tensile strength of the tablets. The hardness of the tablets without flavour was found to be 45.73N, whereas after the addition of various flavours, hardness of the tablets was found to be in the range 24.77 - 31.81N (Table 3.9 and Figure 3.6). The percent weight loss during the friability test was found to be less than 1%. The lower hardness could be due to lower binding effect of flavours.

Overall the porosity of the tablets produced was found to be similar and in the range 27.17 - 29.94%, however, addition of flavours also caused an increase in the DT of the tablets from 12 seconds for the unflavoured tablets, to DT in the range 13.67 - 18.36 seconds for tablets prepared using various flavours (Table 3.9 and Figure 3.6).

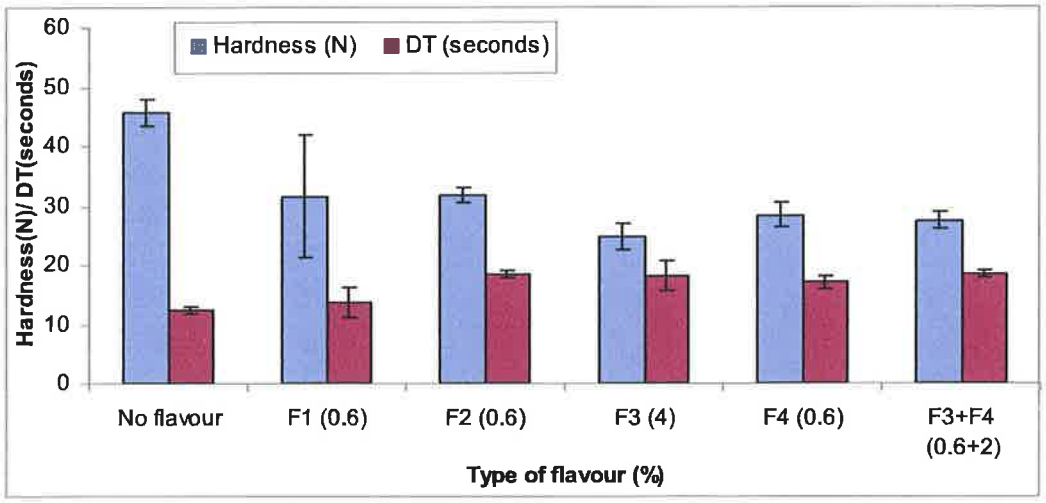


Figure 3.6: Influence of adding various flavours on the hardness and disintegration time of 15mm FBE tablets prepared using M200 as filler, K-CLSF as a superdisintegrant and MgS as a lubricant

3.3. Influence of process variables on the characteristics of FDDTs

Various process variables such as compression force and tablet geometry can affect the characteristics of tablets. The influence of varying compressional forces, tablet size (diameter) and shape on the properties of tablets was evaluated for tablets formulated using either Mannitol 200 or Ludipress®. The disintegrant used was a combination of calcium silicate and SSG, both included at 10%w/w (each) of the formulation. A combination of calcium silicate and SSG was used because from our earlier experiments, tablets containing calcium silicate were found to be friable (Table 3.6), while later in Table 3.7 it was observed that a combination of calcium silicate and SSG formed non-friable tablets. Magnesium stearate was added as lubricant to the tablet blend at 0.5%w/w prior to tableting.

Round toolings of four different diameters i.e. 10mm, 13mm, 15mm and 20mm and two different shapes; flat faced bevelled edge and biconvex were studied as outlined in Figure 3.7. Tableting was carried out on a rotary tablet press at 3 different compressional forces of 10kN, (100-MPa), 15kN (150-MPa) and 20kN (200-MPa).

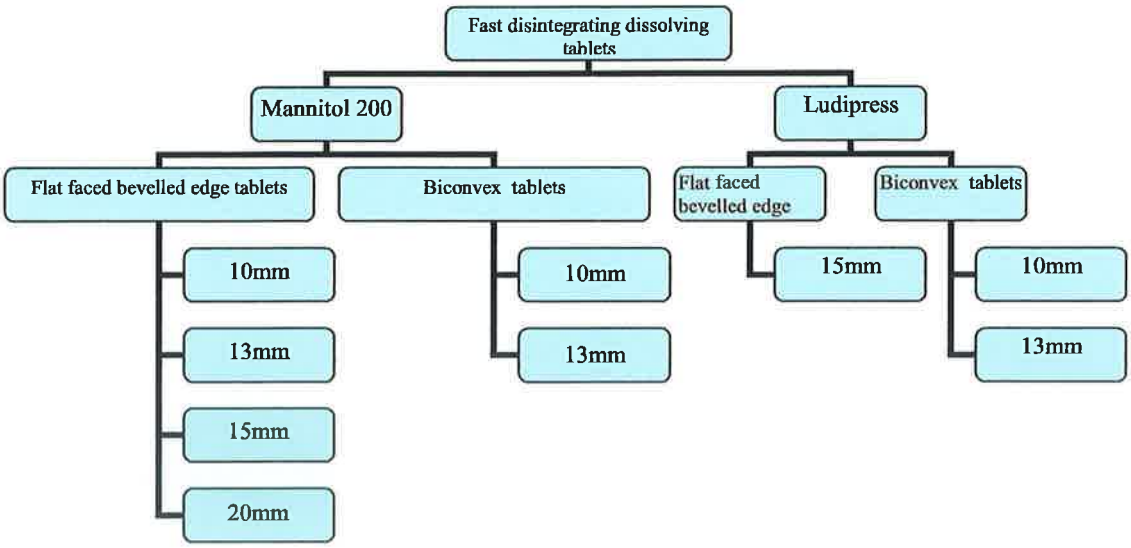


Figure 3.7: Scheme showing the various shapes and size of FDDTs prepared using Mannitol 200 or Ludipress® as filler

3.3.1. Influence of increasing compressional force and tablet diameter on Mannitol round FBE tablets

Compression force is the amount of force required to convert the blend of active and excipients into tablets. An alteration in the compression force can have a profound effect on the characteristics of the tablets in particular tablet hardness and disintegration time. At a particular compression force, the characteristics of the tablets also depend on the constituents of the blend and properties of the material present in the blend. The effect of increasing compressional force on the characteristics of mannitol-based round FBE tablets of varying diameters and tablet weights was evaluated. In this study, four tablet diameters of 10mm, 13mm, 15mm and 20mm at a target weight of 300, 500, 550 and 1000mg, respectively, were compressed at the increasing compressional force of 10kN, 15kN and 20kN.

The influence of increasing compressional force on the characteristics of the tablets is given in Table 3.10. The weight of the tablets was uniform irrespective of the compression force and the tablet diameter. This is related to the excellent flow properties of the Mannitol 200 used.

Table 3.10: Characteristics of Mannitol based FBE tablets formulated at four different diameters of 10mm to 20mm and compression force of 10-20kN

CF* (kN)	TD** (mm)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
10	10	301.29 ± 2.68	45.24 ± 2.49	0.1192	0.17	49.00 ± 2.65	24.97
	13	490.36 ± 3.33	29.78 ± 0.81	0.0512	0.36	37.67 ± 2.08	26.63
	15	551.06 ± 4.79	37.52 ± 1.16	0.0425	0.00	37.33 ± 3.79	30.04
	20	1002.12 ± 6.71	13.68 ± 1.54	0.0132	failed[6]	27.33 ± 2.52	34.90
15	10	298.41 ± 3.49	80.27 ± 3.31	0.2192	0.00	91.33 ± 3.51	18.79
	13	495.83 ± 3.82	54.67 ± 2.59	0.0943	0.00	61.67 ± 5.03	24.97
	15	546.68 ± 0.49	71.43 ± 10.3	0.0816	0.00	37.67 ± 3.79	27.99
	20	996.99 ± 6.08	17.80 ± 1.05	0.0172	failed[6]	27.00 ± 2.00	34.37
20	10	293.45 ± 0.70	100.8 5± 1.7	0.2822	0.00	117.3 ± 2.08	14.87
	13	492.07 ± 2.90	73.52 ± 5.30	0.1291	0.00	70.67 ± 7.02	21.62
	15	541.90 ± 1.79	97.01 ± 6.88	0.1124	0.00	42.00 ± 8.89	24.07
	20	1002.86 ± 6.52	24.97 ± 0.58	0.0243	failed[6]	29.67 ± 0.58	31.00

*compression force, **tablet diameter, [1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6]all tablets broke during the friability test,

A decrease in the thickness of the tablets with an increase in CF from 10 - 20kN was observed for the 10, 13, 15 and 20mm diameter tablets. Tablet thickness decreased from 3.33 to 2.88mm for 10mm, 3.34 to 3.15mm for 13mm, 2.78 to 2.52mm for 15mm and 3.05 to 2.88mm for 20mm tablets.

An increase in tablet compression force led to a considerable increase in tablet hardness (Figure 3.8a). Increasing the compression force (CF) by a multiple of 2, from 10kN to 20kN caused an increase in the hardness of the tablets by a factor of more than 2 for 10mm tablets. A similar increase in hardness for the 13, and 15mm tablets was observed. At the larger diameter of 20mm, an increase in CF caused a comparatively smaller increase in tablet hardness from 13.68 to 24.97N (Figure 3.8a).

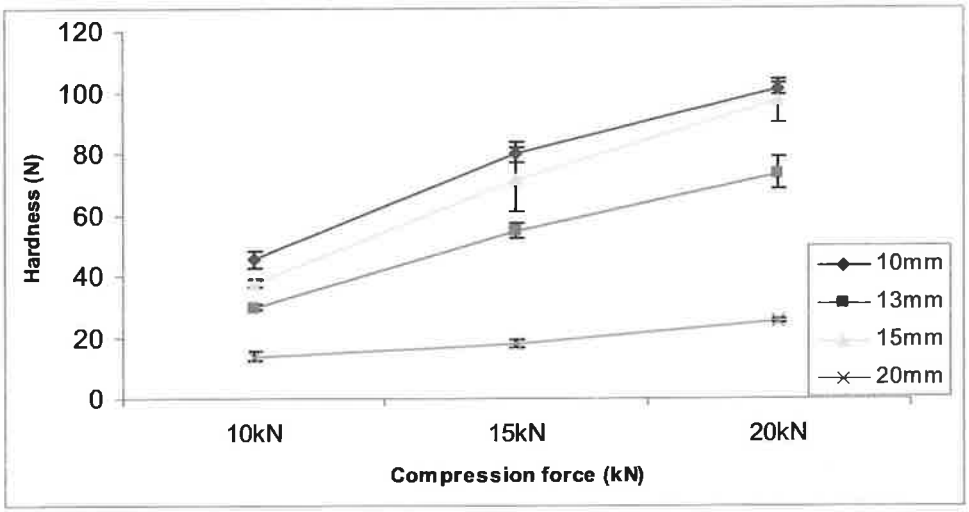


Figure 3.8a: Effect of increasing compressional force on the hardness of round FBE tablets at increasing tablet diameters of 10 - 20mm

DT of the tablets with smaller diameter of 10mm and 13mm was found to be proportional to the compressional force at which the tablets were compressed. With an increase in the compression force from 10 to 20kN for both, a significant rise in the DT of the tablets was observed from 49 - 117.3 seconds for 10mm tablets (ANOVA, $p < 0.0001$) and from 37.67 - 70.67 seconds for the 13mm tablets (ANOVA, $p < 0.001$) (Figure 3.8b). This can probably be

attributed to a decrease in the porosity of the tablets from 24.97 to 14.87% for 10mm and from 26.63 to 21.62% for the 13mm tablets.

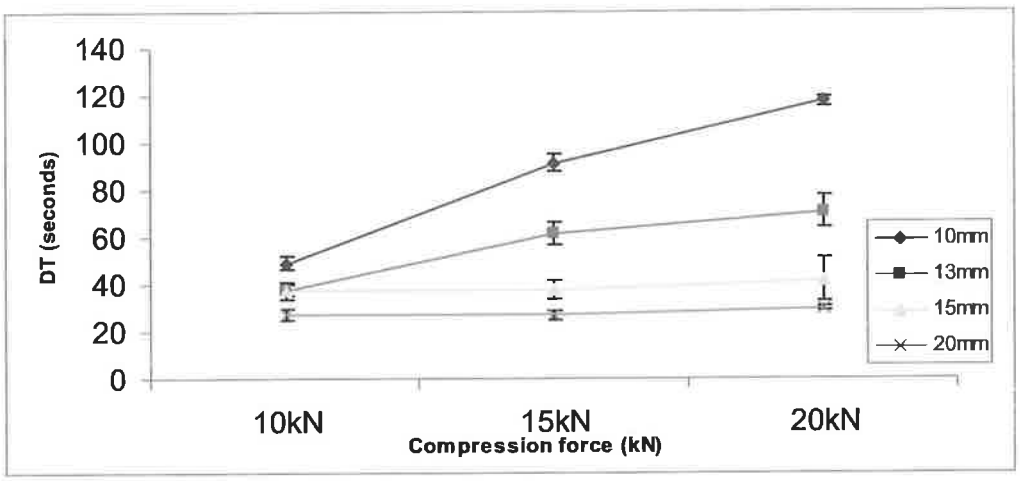


Figure 3.8b: Effect of increasing compressional force on the DT of round FBE tablets at increasing tablet diameters from 10 - 20mm

Tablet formation is the result of densification, inter-particle bonding and relaxation. Therefore, on compression the intermolecular voids would decrease, as a result leading to better binding and densification of tablets. The result is decrease in water penetration, giving high disintegration time with an increase in compressional force (Van Veen et al., 2000).

On the contrary, with an increase in tablet compression force from 10kN to 20kN, for 15mm and 20mm tablets, no noteworthy alteration in the DT of tablets was observed (ANOVA, $p > 0.05$). The DT was found to be in the range from 37.33 to 42 seconds and 27.33 to 29.67 seconds, respectively (Figure 3.8b), despite the decrease in porosity of tablets observed for both 15mm and 20mm tablets. This occurrence can probably be due to relatively larger surface of the 15mm and 20mm tablets in contact with the disintegration medium therefore resisting any alteration in the DT of the tablets.

Abbaspour et al (2008) reported that for the 10mm flat faced tablets consisting of 60%w/w Avicel®, 10%w/w cross-linked PVP and 30%w/w PEG 4000 an increase in the compression force by a multiple of 3, i.e. from 5kN to 15kN caused a 15-fold increase in the DT of the tablets from 1 minute to 15 minutes. A corresponding decrease in friability from 2.6% to 0.05% was also noticed.

The influence of increase in tablet diameter from 10mm to 20mm on the characteristics of tablets was also analysed.
At the compression force of 10kN, as the tablet diameter was increased from 10mm to 20mm, a ten fold decrease in tablet tensile strength was observed from 0.1192 to 0.0132N/mm^2. A similar trend was observed at the higher compression forces of 15kN and 20kN, where the decrease in tensile strength was observed from 0.2192 - 0.0172 at 15kN and 0.2822 - 0.0243N/mm^2 at 20kN (Figure 3.9a).

Similarly, at the compression force of 10kN, an increase in tablet diameter from 10mm to 20mm resulted in a consistent decrease in the DT of the tablets from 49 to 27.33 seconds. While, at the higher compression force of 15kN and 20kN, an increase in tablet diameter from 10mm to 20mm caused a comparatively greater decrease in the DT of tablets from 91.33 to 27 seconds and 117.3 to 29.67 seconds, respectively (Figure 3.9b).
This phenomenon can be due to increase in tablet porosity with an increase in tablet diameter from 10mm to 20mm. The increase in porosity at 10kN compression force was relatively smaller; from 24.97 to 34.90%, while at 15kN and 20kN, the increase in the porosity was greater at 18.79 to 34.37% and 14.87 to 31%, respectively.
The lower DT of the larger diameter tablets was related to their higher porosity.

The friability of all tablets was less than 1%, except for the 20mm tablets where the tablets were found to be fragile at all the compression forces ranging 10 - 20kN, attributed to the low tablet hardness of the 20mm tablets in the range of 13.68 - 24.97N. This was considered to be the result of reduced interparticle bonding, probably due to ineffective compressional force at the highest tablet diameter of 20mm. As the tablet diameter increases from 10 to 20mm, the density of the tablet decreases from 1.2077 to 1.0479g/cc, hence, forming thinner tablets, reflecting the need for the use of higher compressional force as the tablet diameter increases.

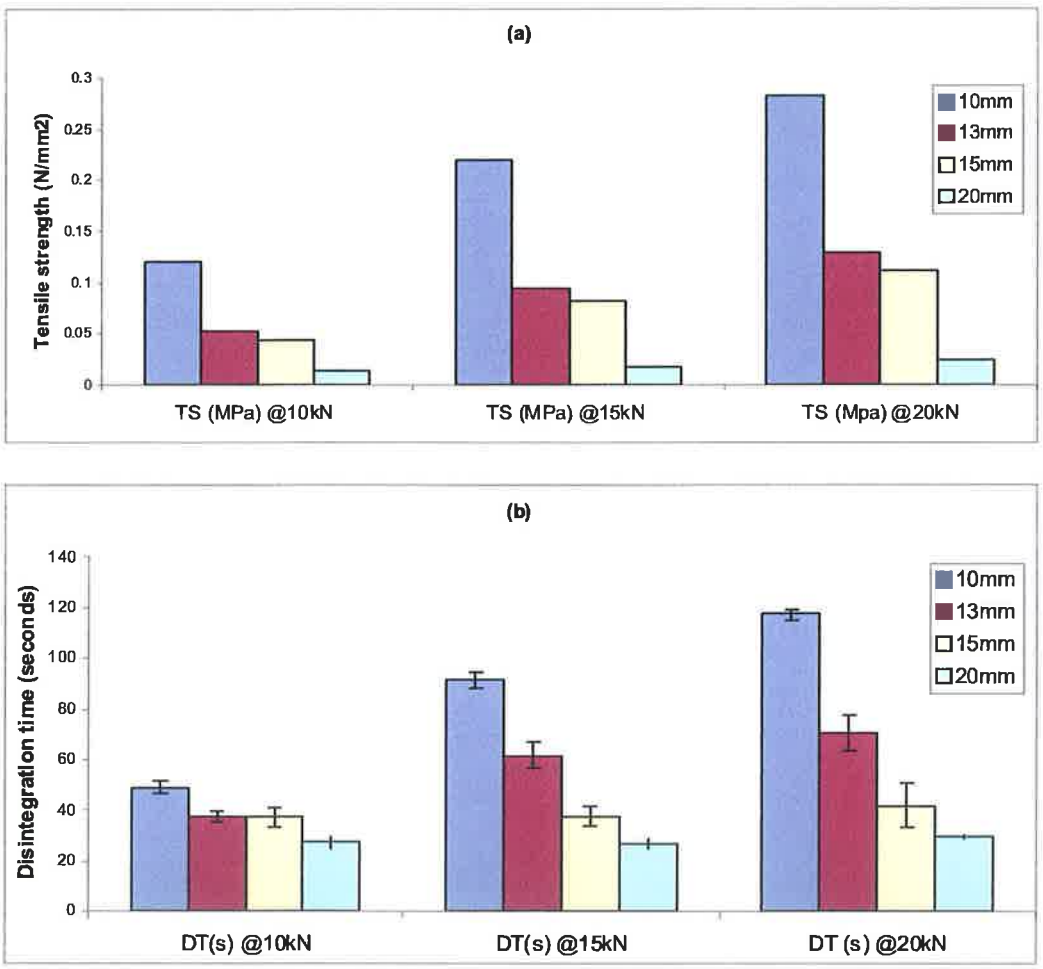


Figure 3.9: Influence of increasing tablet diameter from 10mm to 20mm on the (a) tensile strength and (b) disintegration time of tablets compressed at compression force ranging 10 - 20kN

A pictorial representation of the *in-vitro* DT of tablets at three different diameters 10mm, 13mm and 15mm shown in Figure 3.10 a-c confirms that as the tablet diameter increases the time at which tablets fully disintegrated decreased.

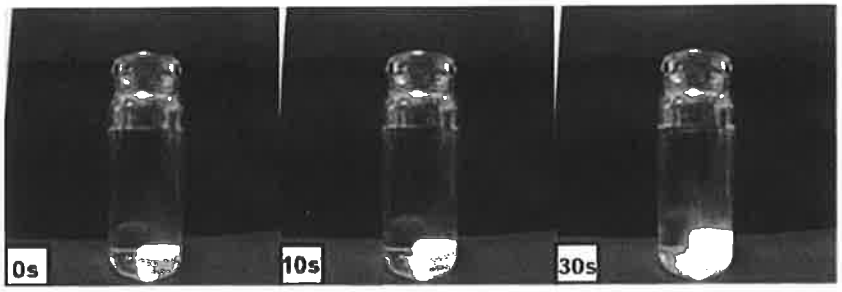


Figure 3.10(a): Disintegration time of 10mm flat faced bevelled edge tablets, with a tablet weight of 200mg

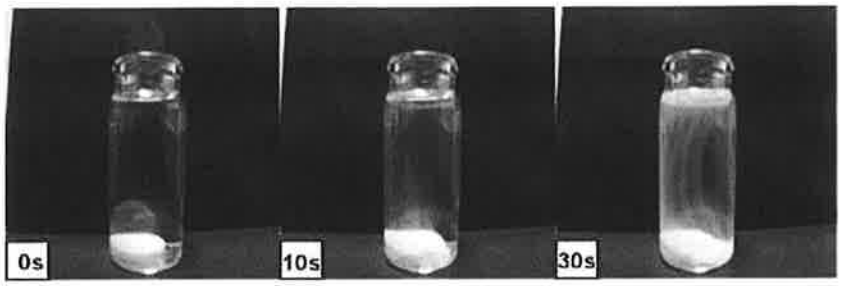


Figure 3.10(b): Disintegration time of 13mm flat faced bevelled edge tablets, with a tablet weight of 300mg

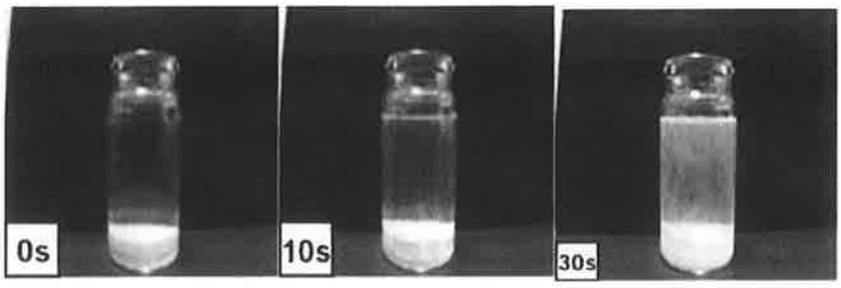


Figure 3.10 (c): Disintegration time of 15mm flat faced bevelled edge tablets, with a tablet weight of 500mg

The effect of increasing CF on Ludipress® FBE tablets of 15mm diameter was also examined, because it was observed earlier in Table 3.4 and 3.5 that Ludipress tablets failed the friability test. An increase in hardness and tensile strength accompanied by a decrease in porosity and an increase in DT was observed similar to corresponding M200 tablets. Compared to the M200 based tablets, the hardness of the ludipress tablets was lower, however the Ludipress® tablets showed a higher DT than the corresponding M200 tablets (Table 3.11). This result was not expected as ludipress is co-processed filler consisting of a binder, Kollidon® 30 and a disintegrant, Kollidon® CL, each at 3.5%w/w. The aqueous solubility of mannitol is 22g/100g, at 20°C while lactose has a low solubility of 18.90g/100g at 25°C. The higher porosity and slightly higher water solubility of Mannitol 200 probably contributed to the fast disintegration of the M200 FDDTs.

Table 3.11: Characteristics of the Ludipress®, 15mm FBE tablets, obtained at three compression force, i.e. 10kN, 15kN and 20kN

Filler	CF (kN)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
Ludipress®	10	575.54 ± 1.61	10.86± 0.72	0.0124	failed[6]	71.67± 3.06	24.75
	15	574.53 ± 1.32	21.60± 2.05	0.0246	failed[6]	88.33± 16.50	24.32
	20	575.6± 1.84	38.73± 2.53	0.0446	failed[6]	93.67± 12.22	20.64
Mannitol 200	10	551.06 ± 4.79	37.52± 1.16	0.0425	0	37.33± 3.79	30.04
	15	546.68 ± 0.49	71.43± 10.3	0.0816	0	37.67± 3.79	27.99
	20	541.90 ± 1.79	97.01± 6.88	0.1124	0	42.00± 8.89	24.07

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6] all tablets broke

3.3.2. Examination of tablet shape and geometry on characteristics of tablets

Compression force applied to toolings and hence tablet blend during tableting is expected to vary depending on the shape of the toolings. In this study the characteristics of tablets at two shapes, round, flat faced bevelled edge (FBE) and biconvex (BC) tablets formulated using a blend of mannitol, CaS, SSG and MgS were compared. The tablets were prepared at both 10mm and 13mm diameter. The tablets were compressed at 10kN at a target weight of 300mg for 10mm tablets and 500mg for 13mm tablets.

The tablets formed were fairly uniform in weight with a maximum variation of 1.85%, independent of the shape of the tablet (Table 3.12).

Table 3.12: Characteristics of the Mannitol 200 FBE and BC tablets at 10mm and 13mm diameters

TD (mm)	Tooling shape	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
10	BC	296.82 ± 5.49	83.98 ± 4.40	0.4324	0.00	105.0 ± 0.04	21.23
	FBE	299.90 ± 5.25	45.24 ± 2.49	0.1192	0.17	49.00 ± 2.65	24.97
13	BC	493.36 ± 3.88	33.89 ± 0.50	0.1183	0.00	107.0 ± 0.07	26.11
	FBE	490.40 ± 3.33	29.78 ± 0.81	0.0512	0.36	37.70 ± 2.10	26.63

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time

The thickness of the biconvex tablets was found to be in the range of 4.03 - 4.49, whereas the thickness of the FBE tablets was lower in the range of 3.28 - 3.34mm.

The characteristics of the tablets were found to be a function of the tablet shape (Figure 3.11). At both diameters examined, hardness and tensile

strength of the biconvex tablets were found to be significantly greater than the flat faced bevelled edge tablets, (10mm, $p < 0.001$ and 13mm, $p < 0.003$). this can be due variable thickness, for instance the biconvex tablets are thicker in the center and thinner at the edges while the FBE tablets have a uniform thickness. FBE tablets also showed a higher friability, though the friability was well below the BP limits of 1%. The higher hardness of the biconvex tablets resulted in a longer disintegration time of above 100 seconds. The DT of the FBE tablets was found to be significantly shorter at below 50 seconds (10mm, $p < 0.0001$ and 13mm, $p < 0.002$).

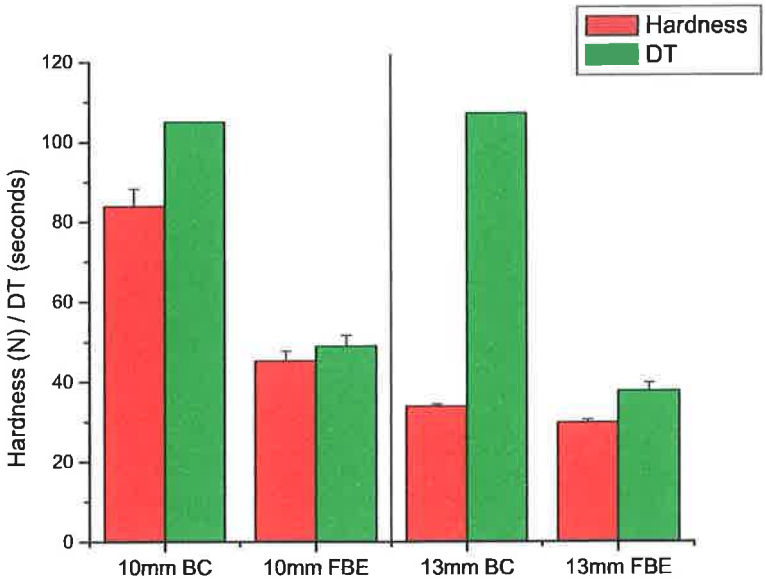


Figure 3.11: Influence of tablet shape on the characteristics of tablets at 10mm and 13mm

Similar results were observed by Heinz et al., (2000), where, at the same compression force, biconvex tablets had a higher tensile strength compared to flat bevelled edge tablets.

3.3.3. Influence of the type of filler and increasing compressional force on characteristics of biconvex tablets

The influence of increasing compressional force from 10 to 20kN on the characteristics of round biconvex (BC) tablets formulated using the lactose-based DC excipient, Ludipress® (Table 3.13) or Mannitol 200 (Table 3.14) was studied at two diameters; 10mm and 13mm. A combination of calcium silicate and SSG at 10%w/w concentration each, were used as the disintegrant and magnesium stearate at 0.5%w/w was added as the lubricant. Tablets formulated showed low weight variability of less than 0.80%, irrespective of the type of filler or compression force employed (Table 3.13 and 3.14). Similar to previous observations for the FBE tablets in Table 3.11, Ludipress® based BC tablets (Table 3.13) had lower hardness and tensile strength which was accompanied by longer DT compared to the M200 BC tablets (Table 3.14). This was observed at both tablet diameters studied. The DT of both Mannitol 200 and Ludipress® tablets was high at > 100 seconds, although Ludipress® tablets showed higher DT.

An increase in the diameter of the tablet from 10 to 13mm resulted in a decrease in the hardness of BC tablets.

Table 3.13: Characteristics of the Ludipress® biconvex tablets compressed at three different compression force and 10mm and 13mm diameter

TD (mm)	CF kN	Weight[1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4]	DT[5] (s)	Porosity (%)
10	10	307.95±0.68	36.69 ±1.11	0.1824	0.65	118.7 ±19.5	21.36
	15	309.37±0.46	71.82 ±2.40	0.3716	0.00	129.0 ±6.08	16.73
	20	309.84±0.25	106.7 ±0.56	0.5577	0.00	135.0 ±2.00	15.45
13	10	532.21±4.79	21.60 ±0.20	0.0751	failed[6]	140.7 ±2.08	20.21
	15	525.86±1.63	36.20 ±6.64	0.1278	failed[7]	139.7 ±17.0	19.36
	20	527.43±1.69	62.02 ±1.16	0.2245	0.00	136.7 ±7.64	16.12

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6] All tablets broke, [7]5 Tablets broke

Table 3.14: Characteristics of the Mannitol 200 biconvex tablets compressed three compression force and 10mm and 13mm diameter

TD (mm)	CF (kN)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)
10	10	296.83 ± 1.87	83.98± 4.40	0.4324	0.00	105.00 ± 4.58	21.23
	15	297.48 ± 0.48	141.5± 6.36	0.7417	0.00	108.67 ± 2.52	19.16
	20	298.11 ± 1.40	191.2± 5.47	1.0180	0.00	103.33 ± 3.51	17.28
13	10	493.36 ± 3.90	33.89± 0.50	0.1183	0.00	107.00 ± 7.21	26.11
	15	491.95 ± 1.53	47.20± 1.08	0.1697	0.00	110.67 ± 8.02	23.38
	20	494.35 ± 3.86	60.39± 1.50	0.2233	0.00	103.00 ± 7.04	19.53

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time

An increase in the compression force from 10 - 20kN caused a decrease in tablet thickness of both, Ludipress® and Mannitol 200 based BC tablets, as expected. At 10mm and 13mm tablets, for Ludipress® tablets the decrease was from 4.08 to 3.88mm and 4.49 to 4.31mm, respectively, while for Mannitol 200 based BC tablets, the decrease was from 3.94 to 3.81mm and 4.47 to 4.22mm, respectively.

As the compression force increased from 10 - 20kN, a 2x increase in the hardness for mannitol based tablets and a 3x increase in hardness for the Ludipress® based tablets was observed (Figure 3.12a and b).

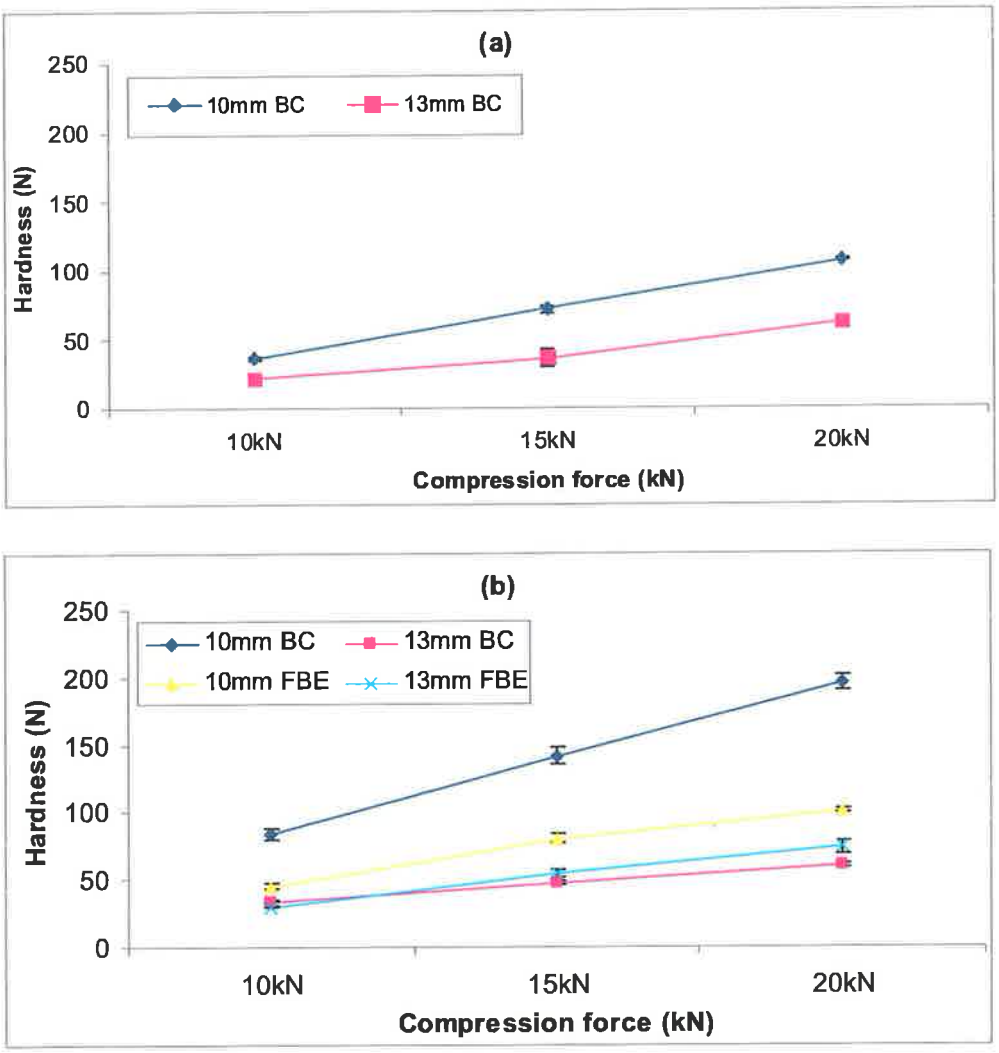


Figure 3.12: Effect of increasing compression force on the hardness of FDDTs containing (a) ludipress and (b) Mannitol 200

Although a decrease in tablet porosity with increasing compressional force was observed for both Ludipress® and mannitol based tablets, at both diameters no significant increase in the DT of the tablets was observed, indicating that DT of the BC tablets was independent of the applied compression force at the tablet diameters examined (Table 3.13 and 3.14).

3.3.4. Influence of tablet weight on characteristics of Mannitol 200 FDDTs

The influence of tablet weight on the characteristics of 10mm and 13mm FBE FDDT was studied. Tablets were formulated using Mannitol 200, K-CLSF, magnesium stearate as lubricant and a combination of raspberry and mint as flavours. The target tablet weight was 200mg and 300mg; and 300mg and 500mg for the 10 and 13mm diameter FBE tablets, respectively. The tablets were compressed at 10kN and at a turret speed of 7rpm. Results shown in Table 3.15 suggest that the tablets formed were uniform with weight with variability of less than 0.5%.

Table 3.15: Influence of increase in tablet weight on the characteristics of 10mm (B030) and 13mm (B052) FBE M200 based tablets

TD (mm)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (s)	Porosity (%)	Thickness (mm)
10	203.52 ± 1.79	50.31± 2.80	0.1422	0.00	16.33± 3.51	19.35	2.35
	302.70 ± 1.18	79.07± 2.31	0.1866	0.33	24.00± 1.73	19.81	3.44
13	303.02 ± 0.83	28.95± 0.55	0.0566	0.66	14.67± 1.53	23.45	2.25
	501.36 ± 2.15	51.50± 0.97	0.0860	0.20	34.00± 3.61	24.00	3.61

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time

An increase in tablet weight at both, 10mm and 13mm FBE resulted in a significant increase ($p < 0.0001$) in hardness and tensile strength with a corresponding increase in the DT of tablets from 16.33 to 24 seconds and 14.67 to 34 seconds for 10mm and 13mm tablets, respectively. A small increase in porosity and an increase in thickness was observed with increasing tablet weight at each diameter studied.

3.4. Conclusions

The influence of various formulation variables such as type of fillers, disintegrants, lubricants and flavours on the properties of FDDTs and process parameters such as compression force, tablet diameter, shape and weight was investigated.

A range of formulation and process parameters giving fast dissolving tablets with desired mechanical properties and fast disintegration were identified.

All the DC fillers used in the present study showed good rheology and therefore contributed to the formulation of tablets which were uniform in weight and of very low weight variation generally < 1.85%. The BP 2008 specification states that for the batch to pass the test of weight uniformity, the percentage deviation allowed for tablets with average weight ≥ 250mg is 5%.

The hardness and tensile strength of cellulose based filler, Prosolv® was found to be higher than for the sugar based fillers and was in the order Prosolv® > Sorbitol > Mannitol 200 > Mannitol 300 > Ludipress® > Mannogem. Of these only Prosolv®, sorbitol and Mannitol 200 showed a percent weight loss of less than 1% during the friability test.

The lowest DT at 5.67 seconds was observed for FDDTs formulated using Mannogem^{TM} EZ. This was expected, given its low hardness of 13.19N. The highest DT was observed for sorbitol at 151.6 seconds.

Tablets formulated with M200 or M300 or Prosolv® showed DT < 20 seconds. M200 or M300 are water-soluble fillers whereas Prosolv® is silicified microcrystalline cellulose (SMCC) containing 2%w/w of colloidal silicon dioxide (SiO2). Silicon dioxide is a commonly used glidant in tablets imparting required flowability to the tablet blend and is reported to impart good disintegration properties to the compacts (Tobyn et al., 1998).

In conclusion, tablets formulated with Mannitol 200 or Prosolv®, besides having good mechanical strength, possessed DT of less than 20 seconds, and therefore were chosen for the further study to evaluate the influence of the type of disintegrant on tablet characteristics.

The choice of disintegrant is very important in the formulation of FDDT in order to achieve low disintegration time. A number of superdisintegrants were investigated in this study based on their disintegration mechanism. The disintegration time of the tablets was found to be a function of the type of disintegrant used. For tablets containing M200, the order of increasing disintegration time was, sodium citrate < calcium silicate < Luquasorb® < K-CLSF < citric acid < SSG. The tablets containing SSG had the highest disintegration time of 36.67 seconds.

The osmotic agents, sodium citrate and citric acid possessed DT of 8.20 and 14.80 seconds, respectively. This is related to their high water solubility and has been utilised in previous proprietary technologies such as DuraSolv®, (Wehling and Schuehle, 1996), OraSolv® (Khankari et al., 2001), as part of effervescent agents included to enhance dissolution. However, a disadvantage is the moisture sensitivity of these excipients which would require controlled humidity conditions during manufacture and storage of tablets containing such excipients.

Calcium silicate (CaS) tablets had a DT of 11 seconds. CaS is a dispersing agent that acts by a wicking mechanism. The tablets generated using calcium silicate were friable.

The low disintegration time for the tablets containing Luquasorb® could be due to its high swelling property. For tablets containing K-CLSF, the low disintegration time could be due to its disintegration mechanism by wicking and little swelling, while the tablets containing SSG possessed the highest disintegration time of 36.67 seconds, which could be due to extensive swelling

accompanied by gelling. The gelling property of SSG may cause occlusion to the tablets pores, hence inhibiting further penetration of water into the tablets that is usually responsible for breaking the bonds between the particles in the tablet, causing disintegration of the tablet.

The three disintegrants Luquasorb®, K-CLSF and SSG were selected and compressed with Prosolv® as the filler. The disintegrants arranged in increasing order of the DT, SSG < K-CLSF < Luquasorb®. Prosolv in combination with Luquasorb® gave the highest DT of 47.67 seconds.

For the superdisintegrant, SSG, it can also be hypothesised that the highest disintegration time for the tablets containing Mannitol 200 and the lowest disintegration time for the tablets containing Prosolv® as filler can be due to the aqueous solubility of mannitol competing with SSG for the available disintegration medium.

Kollidon CLSF was chosen as a preferred superdisintegrant followed by SSG and luquasorb, because K-CLSF was observed to give lower DT for M200 or Prosolv® - based tablets.

The use of hydrophilic lubricant when compared to the hydrophobic lubricant did not reveal any significant difference in terms of tablet characteristics. The DT of the tablets was found to be in the range 19.83 - 32 seconds. Therefore conventionally used hydrophobic disintegrant, magnesium stearate was preferred for the further study.

As fast disintegration tablets are designed to dissolve in the mouth and as most drug compounds have an unpleasant taste, a requirement of fast disintegrating dissolving tablets (FDDTs) is favourable properties of taste and good mouth feel. Various flavours and sweetening agents were therefore added to selected formulations to enhance their palatability and the net result on the tablet characteristics was evaluated. The addition of flavours and

sweeteners at a concentration ranging 0.5 - 4%w/w did not significantly affect the characteristics of the tablet.

The influence of various tableting process variables on the characteristics of the tablets was studied. In the present study, the influence of increasing compression force at three different levels of 10, 15 and 20kN on the mechanical strength and DT of the tablets at various tablet diameter, shape and weight was investigated. Tablet diameters in the range of 10-20mm and at 2 tablet shapes; flat faced bevelled edge round and biconvex round were examined.

The effect of increase in the compression force on the characteristics of the tablets was found to be dependant on the diameter of the tablets. In general, an increase in compression force had a higher affect on the hardness and DT of smaller diameter tablets compared to the larger diameter tablets. The hardness and DT of tablets were found to be directly proportional to the applied compressional force and inversely proportional to tablet diameter for flat faced bevelled (FBE) tablets. Similarly for biconvex (BC) tablets, the tablet hardness was proportional to compression force and inversely proportional to the tablet diameter.

When relating to compression force applied per unit surface area, an increase in compression force from 10 to 20kN causes an increase in compression force per unit surface area at 10mm from 0.1274 to 0.2548 kN/mm^2. A similar increase was observed for 13mm, 15mm and 20mm tablets from 0.0754 to 0.1507 kN/mm^2, 0.0566 to 0.1132 kN/mm^2 and 0.0318 to 0.0637 kN/mm^2, respectively.

As the tablet diameter increases from 10mm to 13mm to 15mm and 20mm, at 10kN, the compression force applied per surface area decreases from 0.1274 to 0.0754, to 0.0566 and 0.0318 kN/mm^2. Similarly, at 20kN the decrease was from 0.2548 to 0.1507 to 0.1132 and 0.0637 kN/mm^2, respectively.

Interestingly, the DT of the BC tablets was found to be independent of the compressional force and tablet diameter.

At similar compressional forces, the FBE tablets possessed lower hardness, tensile strength and disintegration time compared to the BC tablets. The disintegration time for the FBE tablets was found to be below 49 seconds, while for the BC tablets the DT was > 1 minute, which was related to the lower hardness and higher porosity of the FBE tablets. This can probably be due to the fact that at 10mm or 13mm, the biconvex tablets have higher density 1.2679g/cc and 1.1893g/cc, compared to the respective density of 1.0277 and 1.1809g/cc for 10 and 13mm FBE FDDTs.

An increase in tablet weight by 50% for the 10mm and 13mm tablets resulted in a corresponding increase in both, hardness and DT.

To summarize, the placebo formulations based on Mannitol 200 or Prosolv® in combination with the superdisintegrants SSG, Luquasorb® or Kollidon® CLSF; lubricant, magnesium stearate; and compression force 7-10kN for toolings 10-15mm were found to generate, in particular, FBE tablets with high mechanical strength and low DT in the range 2 - 49 seconds.
In addition, since the tablets passed the friability test with percent weight loss of <1%, such tablets do not require special handling or packaging conditions and can be shipped in conventional low cost packages, and at the same time retain its rapid disintegration or dissolution properties. In this chapter, it was also demonstrated that tablets can be prepared at various tablet diameters which can be useful to accommodate a wide range of doses of the therapeutic agents

Therefore, these formulations were selected and applied to two model drugs.
The addition of API can affect the characteristics of the tablets. It has been demonstrated by Yang et al (2004) that addition of the hydrophobic drug, ketoprofen causes an increase in the disintegration time of the tablets. While, Rawas-Qalaji et al., (2006) reported that addition of the hydrophilic drug, epinephrine, decreases the DT of the tablets.

In the next chapter, chapter 4, the influence of including a hydrophobic drug, diclofenac sodium (DFS) on the characteristics of mannitol-based FDDTs was examined. The DFS was added in its original form, as received and in the form of modified release microparticles prepared by spray drying.

CHAPTER 4

Formulation and characterisation of FDDTs containing diclofenac sodium as unencapsulated and microencapsulated drug

4.0 Introduction

Diclofenac sodium (DFS) was chosen as a model drug in the present study for the formulation of drug loaded fast disintegrating dissolving tablets (FDDTs). DFS has a low oral bioavailability (60%) and a relatively short plasma half life of 1-2 hours, therefore requiring multiple dosage regimens. DFS possesses an unpleasant taste requiring taste masking and in addition, oral administration of immediate release formulations of DFS has been known to cause gastrointestinal disturbances. These have led to the development of controlled release forms, providing an initial burst of drug to facilitate rapid onset of action and then maintaining a constant plasma drug level for a prolonged period of time, which is desirable for optimum delivery and safety in addition to providing taste masking (Al-Omran et al., 2002; Ganza-Gonzalez et al., 1999; Katzung et al., 1998; Rattes and Oliveira, 2007; Sajeev et al., 2002; Wilson and Gisvold, 1962).

DFS was formulated as immediate release FDDT formulation using the API as received and as sustained release (SR) FDDT using the DFS microparticles, prepared by spray drying with ethylcellulose (EC) as sustained release polymer. The influence of formulation and spray drying process variables on the morphological, rheological and drug release properties of the microparticles were studied. The size of microparticles prepared by spray-drying can range from a few microns to several tens of microns and with a relatively narrow size distribution (Esposito et al., 2000; Huang et al., 2003). This size range is desirable for inclusion into FDDT formulations for palatability and good mouthfeel. In addition spray drying is known to result in the formation of free flowing particles which allows ease of further processing into suitable dosage forms such as capsules and tablets for administration to patients (Gursoy et al., 1999; Lin and Kao, 1991).

Selected microparticles were subsequently used to formulate fast disintegrating dissolving tablets using mannitol based placebo formulations identified in Chapter 3.

4.1. Results & Discussion

4.1.1 Examination of processing and formulation factors on the characteristics of DFS/EC microparticles prepared by spray drying

Solutions of diclofenac sodium (DFS) with and without ethylcellulose (EC) in ethanol were spray dried using a conventional Buchi mini spray dryer B290 as described in Chapter 2, section 2.1.2. Feed solutions containing 10%w/v of total solid, at a drug to polymer ratio of 25:75 were used. The influence of spray drying process parameters such as spray flow rate (SFR), that controls the quantity of nitrogen (air) which disperses the feed solution, the formulation feed flow rate (FFR), and the air aspiration rate (AAR) which quantifies the drying medium flowing through the spray drying chamber, on particle properties were first investigated. The addition of a plasticizer and increasing the inlet temperature (Tinlet, °C) on the particle characteristics and drug release properties of the particles were also studied.

The spray drying process parameters and formulation variables studied are given in Table 4.1. The outlet temperature (Toutlet, °C) for all the batches was monitored and was found to be within the temperature range of 40 - 60°C for all batches studied (Table 4.1). The lowest outlet temperature of 40°C was recorded when the lowest AAR of 65% was used, while the highest outlet temperature of 60°C was observed when the higher inlet temperature of 100°C was used.

Table 4.1: Formulation and process parameters used for the spray drying of DFS/EC microparticles

Variable	Batch	Plasticizer	T_{inlet} (°C)	AAR (%)	SFR (Nl/hr)	FFR (ml/min)	T_{outlet} (°C)
DFS - API	-	Nil	80	86	400	9.6	40
Spray flow rate (SFR)	RP08	Nil	80	86	400	9.6	46
	RP15	Nil	80	86	350	9.6	46
	RP16	Nil	80	86	300	9.6	51
Feed flow rate (FFR)	RP08	Nil	80	86	400	9.6	46
	RP11	Nil	80	86	400	6.9	48
	RP12	Nil	80	86	400	4.3	50
Air aspiration rate (AAR)	RP08	Nil	80	86	400	9.6	46
	RP04	Nil	80	75	400	9.6	42
	RP10	Nil	80	65	400	9.6	40
Addition of plasticizer	RP16	Nil	80	86	300	9.6	51
	RP17	Tween 20	80	86	300	9.6	57
	RP18	Lutrol 127	80	86	300	9.6	55
Air drying temperature	RP17	Tween 20	80	86	300	9.6	57
	RP19	Tween 20	100	86	300	9.6	60

4.1.2. Effect of spray drying process variable on the characteristics of spray dried DFS/EC microparticles

First, the effect of spray drying a solution of DFS in ethanol was examined. A significant decrease in the median particle size of DFS was observed; the D50% of DFS was reduced from 8.50 to 3.73µm (Table 4.2), probably due to spraying mechanism during spray drying. Spray dried DFS had a D90% of 122.1 ± 99.7µm and the span value of 30.78 ± 24.98 suggesting a high degree of particle agglomeration on spray drying. This may be related to the hydrophobic nature of DFS and inefficient drying evident during TGA studies outlined below.

Table 4.2: Characteristics of non spray dried and spray dried DFS

API/ Product	Particle size distribution (μm)			SPAN	Microparticle Yield (%)
	D10%	D50%	D90%		
DFS API	1.64 ± 0.05	8.50 ± 0.54	95.33 ± 9.02	11.01 ± 0.38	N/A
SD DFS	0.83 ± 0.87	3.73 ± 0.39	122.1 ± 99.7	30.78 ± 24.98	76 %

Electron microscopy of DFS and spray dried DFS (Figure 4.1) show a change in crystal morphology on spray drying. The SD DFS (b) appeared as fine needles with a high degree of agglomeration as noted by particle size analysis, D90% of 122.1μm and span of 30.78.

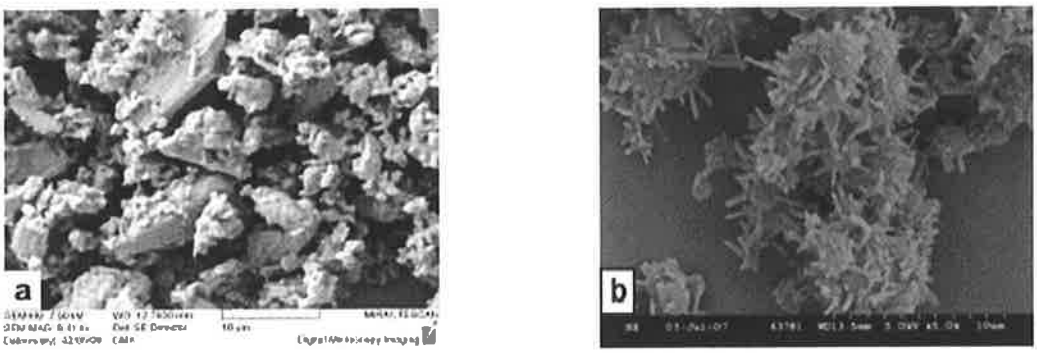


Figure 4.1: Electron micrographs of, (a) non spray dried and (b), spray dried diclofenac sodium

Thermogravimetric analysis (TGA) of the spray dried DFS showed the presence of residual moisture/solvent. A weight loss of 0.297% was observed for the spray dried DFS. In comparison, a weight loss of 0.023% was observed for its non-spray dried version.

The peak melting temperature from the DSC thermograms of the DFS before and after spray drying was found to be 292.99°C and 290.06°C (Figure 4.2), respectively. The values observed are similar to the melting point value of

287°C for non spray dried DFS reported by Pasquali et al., (2007) and 296°C reported by Viitanen et al., (2006). DFS was found to degrade after melting, consistent with literature reports (Cwiertnia et al., 1999). Spray drying is well-known to convert crystalline substance into an amorphous form. Given that DFS has high a melting point of > 285°C, ideally it should have a high Tg of atleast more than 37°C, hence it was interesting to note that spray dried diclofenac sodium was found to be in a crystalline form.

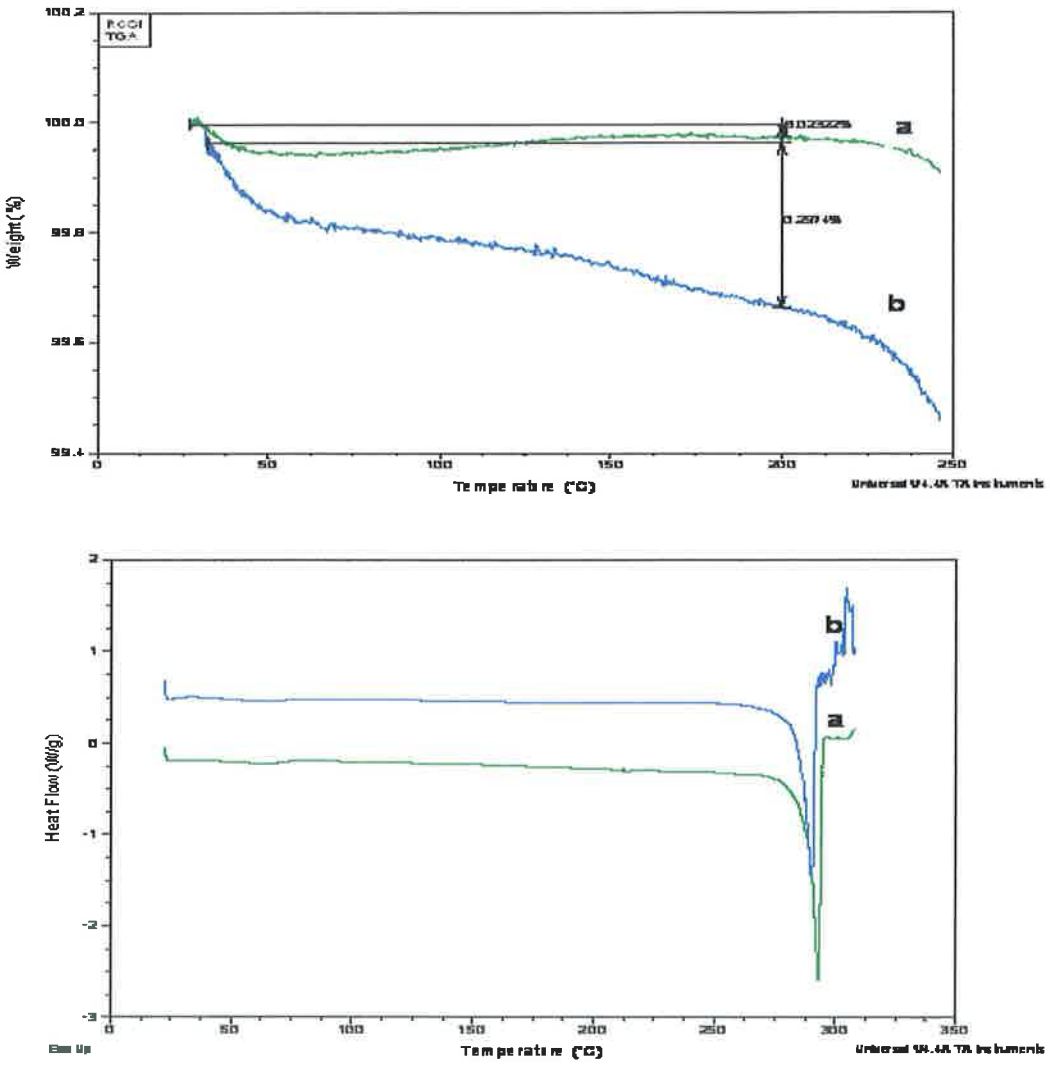


Figure 4.2: TGA and DSC thermogram of (a) non spray dried and (b) spray dried diclofenac sodium

Microencapsulation of diclofenac sodium with ethylcellulose

Diclofenac sodium (DFS) was microencapsulated by spray drying at three spray flow rates (SFR) of 400, 350 and 300 (Nl/h), and the characteristics of the microparticles formed were investigated. From the data in Table 4.3., and Figure 4.3a, SFR was the only variable affecting particle size. A decrease in SFR resulted in an increase in microparticle size for D10%, D50% and D90%. A high SFR results in more efficient nebulisation of the feed solution resulting in smaller droplets and hence smaller particles formed (Prinn et al., 2002).

Table 4.3: Influence of spray drying (SD) parameters on the particle size distribution

SD variable	Batch	Variable level	Particle size distribution (μm)			SPAN
			D10%	D50%	D90%	
SFR (Nl/h)	RP08	400	2.84 ± 0.50	11.05 ± 1.03	36.00 ± 0.87	3.02 ± 0.24
	RP15	350	3.30 ± 0.15	17.92 ± 0.48	52.94 ± 1.24	2.77 ± 0.04
	RP16	300	6.51 ± 0.23	31.60 ± 1.35	103.32± 23.7	3.05 ± 0.65
FFR (ml/min)	RP08	9.6	2.84 ± 0.50	11.05 ± 1.03	36.00 ± 0.87	3.02 ± 0.24
	RP11	6.9	2.72 ± 0.32	11.43 ± 0.54	39.32 ± 0.21	3.21 ± 0.18
	RP12	4.3	2.66 ± 0.13	12.51 ± 0.43	81.70 ± 17.98	7.02 ± 0.59
AAR (%) (m^3/h)	RP08	86 (34)	2.84 ± 0.50	11.05 ± 1.03	36.00 ± 0.87	3.02 ± 0.24
	RP04	75 (30)	3.21 ± 0.18	11.91± 0.299	30.12 ± 0.324	2.26 ± 0.06
	RP10	65 (26)	3.43 ± 0.38	12.88 ± 0.44	40.47 ± 2.22	2.88 ± 0.26

As the SFR was decreased from 400 to 300 Nl/h, an increase in median particle size from 11.05μm to 31.60μm was observed (Table 4.3). As the SFR increased from 350 to 400, the decrease in particle size was lower than at the lower SFR rate of 300Nl/h. He et al (1999) prepared chitosan microspheres by aqueous spray drying and reported that an increase in the spray flow rate from 360 to 600Nl/hr caused an minor decrease in particle size from 3.81 to 3.32μm.

The product yield decreased from 59.5 to 27.3% with decreasing SFR from 400 to 300 Nl/h, Figure 4.3b. This can be due to settling of the larger particles into the spray drying chamber instead of getting carried away into the cyclone separator and collecting vessel.

A decrease in the feed flow rate (FFR) from 9.6ml/min to 4.3ml/min, resulted in a small increase in the median microparticle size from 11.05 to 12.51μm. At the lowest FFR of 4.3ml/min, a high D90% and span value was observed indicating possible particle agglomeration at that flow rate (Table 4.3). A decrease in the FFR from 9.6 to 4.3ml/min, resulted in a corresponding decrease in the product yield from 60 to 49%. Interestingly, Esposito et al., (2000) used hydroalcoholic solvent to prepare Eudragit® microparticles and reported that a ten fold increase in feed flow rate from 0.5 to 5ml/min, caused approximately a three fold increase in the particle size from 3.53 to 10.96μm, with a decrease in the product yield from 48 to 38%.

Varying the air aspiration rates (AAR) from 86% ($34m^3/h$) to 65% ($26m^3/h$) resulted in a small increase in median particle size from 11.05 to 12.88μm. On the contrary, Esposito et al., (2000) reported that an increase in the air aspiration rate from 28 to $35m^3$/hour led to an increase in particle size from 3.53 to 5.59μm. In our studies, a decrease in AAR resulted in a decrease in the percentage yield from 59.45% to 35% (Figure 4.3b).

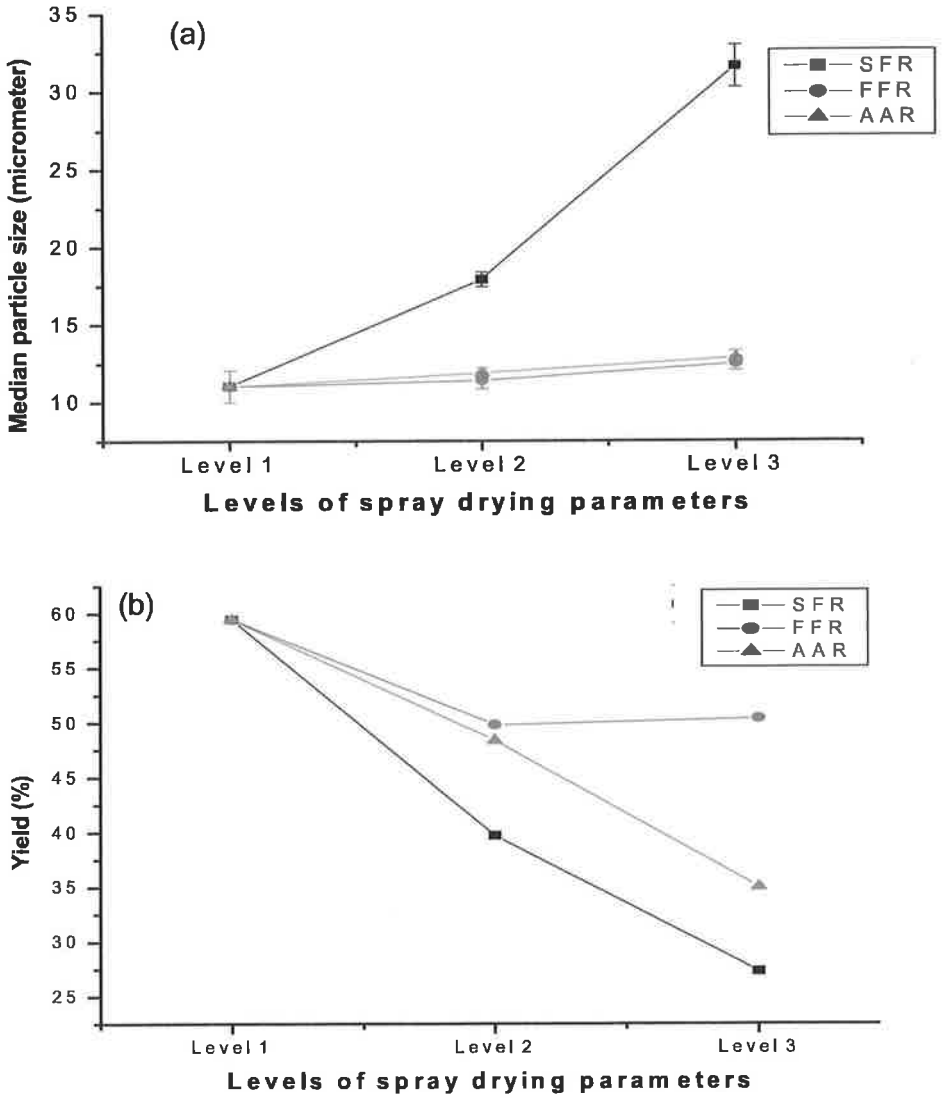


Figure 4.3: Influence of spray flow rate (SFR), feed flow rate (FFR) and air aspiration rate (AAR) on (a) median particle size and (b) yield of DFS/EC microparticles

SD Parameter	Level 1	Level 2	Level 3
SFR (Nl/h)	400	350	300
FFR (ml/min)	9.6	6.9	4.3
AAR (%)	86	75	65

4.1.2.1. Morphology of microparticles

Electron micrographs, Figure 4.4i (a-c), of the spray dried microparticles showed that a decrease in spray flow rate (SFR) from 400 to 300Nl/h resulted in an improvement in the morphology of the microparticles. At the low SFR of 300Nl/h, spherical particles associated with smooth surface were observed. On the contrary, a decrease in the feed flow rate (FFR) of the drug and polymer solution from 9.6 to 4.3ml/min resulted in microparticles with less defined morphology and associated with agglomerate formation (Figure 4.4ii (a-c)). Similar to the effect of decreasing FFR, a decrease in AAR resulted in agglomerated microparticles, particularly at the AAR of 65%. Interestingly, at median AAR of 75%, microparticles produced showed improved morphology with smooth and spherical microparticles formed (Figure 4.4iii (a-c)).

Figure 4.4i SD microparticles produced at SFR of (a) 400Nl/h, (b) 350Nl/h and (c) 300Nl/h

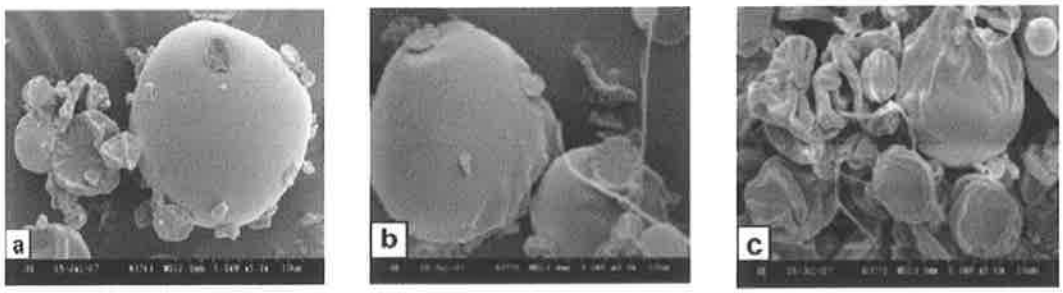


Figure 4.4ii SD microparticles produced at FFR settings of (a) 9.6ml/min, (b) 6.9ml/min and (c) 4.3ml/min

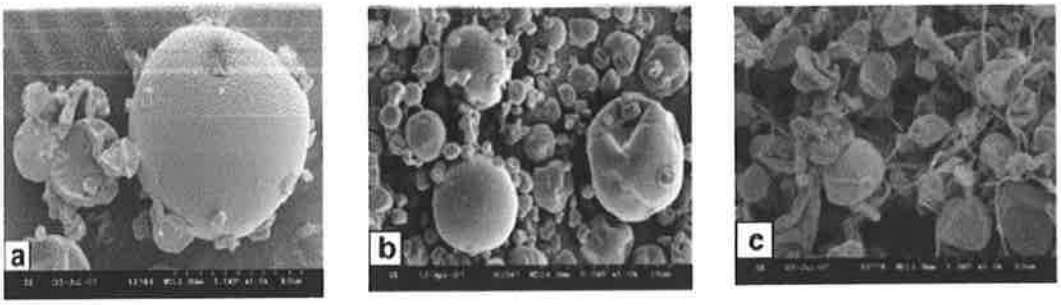


Figure 4.4iii SD microparticles produced at AAR of (a) 86%, (b) 75% and (c) 65%

4.1.2.2. Rheology of microparticles

Good rheological properties are critical during formulation of microparticles into a suitable oral dosage form such as tablets/capsules as they affect uniformity of dosage weight and drug content. The results presented in Table 4.4 demonstrate that spray drying of the drug DFS API resulted in enhancement in its rheological properties, probably attributed to the granular crystalline or aggregate morphology of the spray dried DFS (Figure 4.1b).

For DFS/EC microparticles formulated, a decrease in bulk density was observed with a decrease in SFR and FFR examined. This was accompanied by improved flow properties of the microparticles (Table 4.4). This can be related to the formation of product with greater median particle size or spherical morphology of the microparticles.

A decrease in bulk density can indicate decrease in the number of voids and hence better compaction properties (Bolhuis G & Zuurman K, 1995; Goula and Adamopoulos, 2005; Johansson B and Alderborn G, 2001; Masters, 1985).

On the contrary, a decrease in AAR did not result in a change in bulk density, however a decrease in the Carr's index and thus improvement in the rheology was observed, although the flow properties were poor at all AAR examined. A

low AAR indicates relatively longer residence time of the microparticles in the spray drying chamber, hence longer contact time with the drying medium i.e. high temperature and is associated with improved flow (Esposito et al., 2000; Huang et al., 2003).

Table 4.4: Influence of the variation in spray drying variables at various levels on the density and flow character of the spray dried product

Spray drying variable	Levels	Rheological attributes			
		ρ_b (g/cc)	ρ_t (g/cc)	CI (%)	Flowability [1]
DFS (API)	-	0.317±0.00	0.382±0.04	17.12	Fair
SD DFS	-	0.180±0.00	0.185±0.01	02.49	Excellent
Spray flow rate (Nl/h)	400	0.122±0.01	0.197±0.01	38.07	Very poor
	350	0.103±0.00	0.138±0.00	25.36	Passable
	300	0.096±0.00	0.138±0.00	30.43	Poor
Feed flow rate[1] (ml/min)	9.6	0.122±0.01	0.197±0.01	38.07	Very poor
	6.9	0.113±0.01	0.163±0.01	30.67	Poor
	4.3	0.110±0.00	0.147±0.01	25.17	Passable
Air aspiration rate (%)	86	0.122±0.01	0.197±0.01	38.07	Very poor
	75	0.114±0.00	0.172±0.00	33.72	Very poor
	65	0.123±0.00	0.183±0.01	32.79	Very poor

[1] flowability was designated as per the scale of flowability outlined in the BP 2008

4.1.2.3. Assayed drug loading (ADL), encapsulation efficiency (EE) and drug release studies from microparticles

The assayed drug loading for all the microparticles formulated was found to be within the range of 22.48 - 27.2%w/w giving encapsulation efficiency in the range 89 - 109% (Table 4.5). The high encapsulation efficiency demonstrates that there was no loss of drug during spray drying, as expected.

The cumulative percent of drug released against time profiles for the microparticles produced was plotted and is presented in Figure 4.5. The drug release was calculated on the basis of the actual drug content.

The Figure 4.5 presents the drug release profiles from the SD microparticles produced at three different SFR, Figure 4.5a, FFR, Figure 4.5b, and AAR Figure 4.5c. In general, the release of DFS from the microparticles was sustained over at least 7 hours following a high initial burst release of 40 - 72% within the first 30 minutes.

Percent drug released within the first 30 minutes (Table 4.5) was found to increase from 48.63 to 53.73% when the SFR was decreased from 400Nl/h to 300Nl/h, probably due to inefficient film formation due to drying of the bigger droplets formed during spray drying.

No change in initial burst release was observed when the FFR was decreased from 9.6 to 6.3ml/min. Subsequently, when FFR was decreased from 6.9 to 4.3ml/min, the initial burst release decreased to 42.79%.

When AAR was decreased from 86 to 75%, an increase in initial burst release was observed from 48.63 to 71.68%, this subsequently decreased to 40.37% at AAR of 65%. A decrease in AAR indicates more residence time in the spray drying chamber, thus better drying and ethylcellulose film formation, hence better sustained release properties.

Table 4.5 Influence of alteration in various spray drying variables on the assayed drug loading (ADL), encapsulation efficiency (EE), and initial DFS release from microparticles, theoretical drug loading of 25%w/w

Spray drying variable	Batch	Levels	ADL (%)	EE (%)	Initial burst release @ 30minutes (%) of assayed DFS
SFR (Nl/h)	RP08	400	22.88	91.52	48.63
	RP15	350	22.48	89.92	52.79
	RP16	300	24.04	96.16	53.73
FFR (ml/min)	RP08	9.6	22.88	91.52	48.63
	RP11	6.9	25.12	102.08	48.90
	RP12	4.3	26.68	106.72	42.79
AAR (%)	RP08	86	22.88	91.52	48.63
	RP04	75	27.20	108.8	71.68
	RP10	65	24.48	97.92	40.37

The high initial burst release is expected as the microparticle size is small and with high drug loading (He et al., 1999).

Ramtoola et al., (1992) reported that for PLA microspheres of size 60 - 70μm, the initial burst release of fluphenazine increased from 10 to 70%, with an increase in drug loading from 10 to 30%.

A sustained release profile over the next 6.5 hours was observed with 74.76 - 97.67% of DFS released. Decreasing SFR resulted in an increase in total drug release at 7 hours to 97.67%. This increase was higher than for other microparticles formulated at varying FFR or AAR, where the maximum amount of drug released was 83.99% (Figure 4.5).

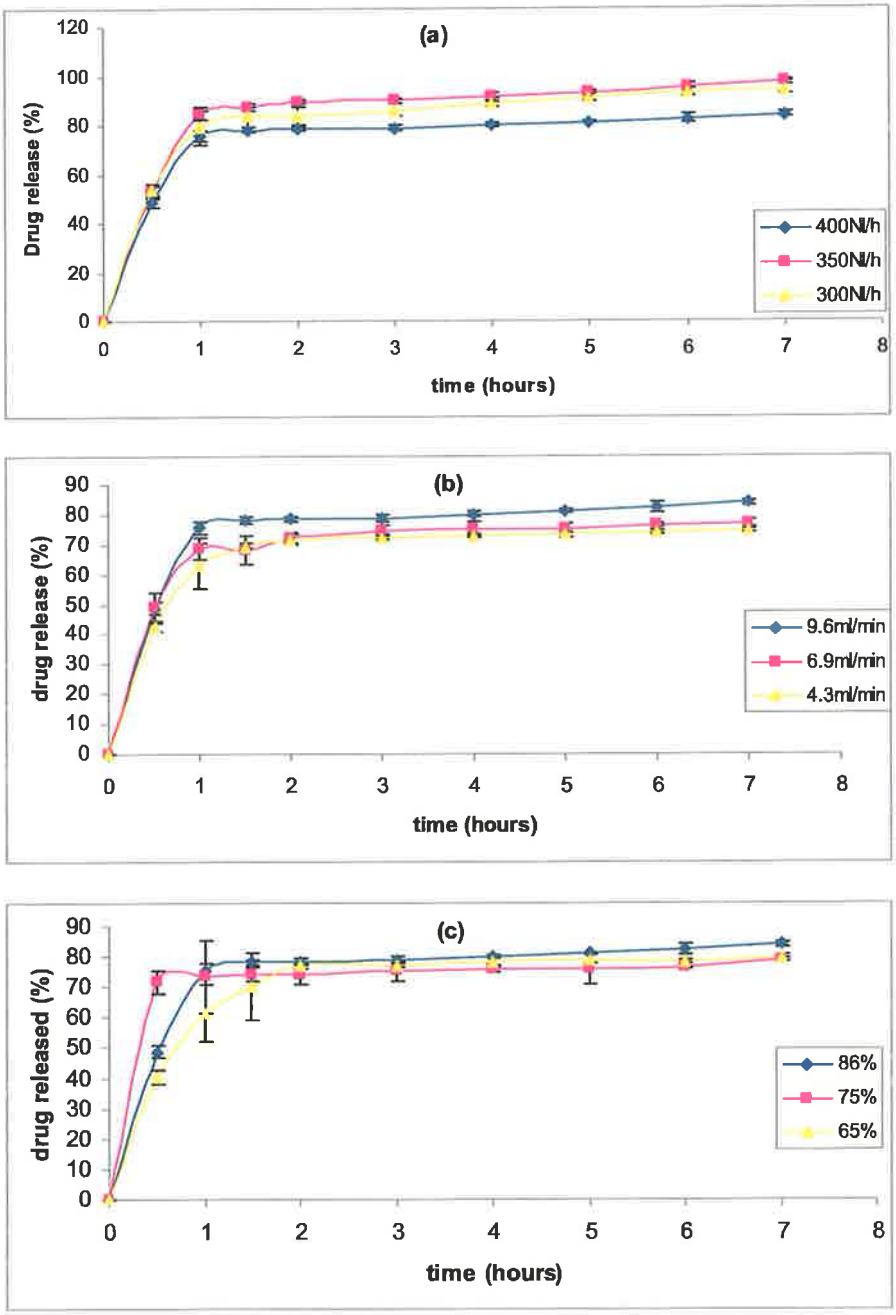


Figure 4.5: DFS release against time profiles for microparticles produced using varying spray drying parameters (a) SFR, (b) FFR and (c) AAR

The DFS release from the microparticles was fitted to the Peppas model (equation 2.15, Chapter 2). It was observed that the Peppas model provides a good fit of the data as indicated by high correlation coefficient (r^2), in the range 0.746 - 0.904. The magnitude of the release exponent "n" in the Peppas equation, regarded as an indicator of the drug release mechanism was calculated and is shown in Table 4.6. The value of n was ≤0.43, in the range 0.148 - 0.201. This indicates that the mode of transport of drug through the polymeric matrix was predominantly controlled by Fickian diffusion kinetics which was expected for the DFS in ethylcellulose (EC) microparticle matrices formulated in this study.

The high value of release constant (k) for microparticles produced at AAR of 75% is an indication of the high level of initial burst release.

Table 4.6: Mathematical modelling describing drug release from the microparticles produced at various spray drying parameters

Spray drying variable	Batch	Levels	Peppas model ($Q = k t^n$)		
			k	n	r^2
Spray flow rate (Nl/h)	RP08	400	33.70	0.151	0.746
	RP15	350	34.29	0.170	0.780
	RP16	300	34.55	0.174	0.862
Feed flow rate (ml/min)	RP08	9.6	33.70	0.151	0.746
	RP11	6.9	34.92	0.148	0.841
	RP12	4.3	32.52	0.166	0.794
Air aspiration rate (%)	RP08	86	33.70	0.151	0.746
	RP04	75	67.86	0.049	0.904
	RP10	65	26.10	0.201	0.808

Bigger particles would mean less amount of free drug, hence better sustained release profile. For batch RP16 that showed a larger D50% at 31.60µm, attempts to optimize this formulation were carried out to improve the controlled release profiles, while maintaining the high drug loading of 25%w/w for further processing into FDDTs.

According to literature reports (Rekhi and Jambhekar, 1995), ethanolic solutions of EC tend to form fragile films which may easily disrupt, allowing high initial burst release of the drug and poor sustained release profile. In addition, EC possesses a relatively high Tg value of 135°C and as a consequence, EC does not readily tend to form flexible films, hence plasticizers have been utilised to improve the flexibility of EC films.
The effect of incorporation of plasticizer to the DFS/EC feed solutions was therefore examined in order to decrease the initial burst release of DFS and improve the sustained release profiles of the DFS/EC microparticles. The addition of a plasticizer may also improve the flexibility and plasticity of the microparticles which can be beneficial in providing resistance to distortion during subsequent compression into final FDDT dosage forms (Dashevsky et al., 2004).

4.1.3. Influence of addition of plasticizer on the characteristics of spray dried DFS/EC microparticles

Two plasticizers were investigated; polysorbate 20 (Tween® 20), a polyoxyethylene derivative of sorbitan monolaurate and Poloxamer 407 (Lutrol® F127), consisting of polyoxyethylene (POE) and polyoxypropylene (POP) units. The effect of inclusion of the plasticizer, at 0.6%w/w concentration of the polymer on the characteristics of SD microparticles was evaluated. The higher or lower concentrations were not evaluated due to time constraints. The process parameters that were found to result in microparticles with the larger particle size, D50% of 31.60µm, were used. These parameters were SFR of 300 (Nl/h), FFR of 9.6ml/min and AAR of 86%.

The addition of plasticizer caused a significant increase (ANOVA; $p < 0.0001$) in all microparticle dimensions, D10%, D50% and D90% (Table 4.7 and Figure 4.6). Microparticle size increased in the order of, no plasticizer < Tween 20 < Lutrol 127. A corresponding decrease in the product percentage yield was observed, the yield decreased from 27.3% for no plasticizer to 13 and 8.5% for Tween 20 and Lutrol F127,

respectively. The bigger particles were observed to be settled in the spray drying chamber instead of getting carried away to the cyclone separation and into the collecting vessel, probably due to a lower AAR of 86%. This explains the low product yield recovered.

Table 4.7: Characteristics of SD microparticles produced without plasticizer (RP16) and with the addition of plasticizers, Tween 20 (RP17) and Lutrol F127 (RP18)

Plasticizer	Particle size distribution (μm)		SPAN	Yield
	D10%	D50%		(%)
Nil	06.51 ± 0.23	31.60 ± 1.35	3.05 ± 0.65	27.3
Tween 20	11.26 ± 0.35	36.62 ± 0.76	2.09 ± 0.05	13.0
Lutrol F127	17.51 ± 0.08	50.83 ± 0.52	2.10 ± 0.16	8.50

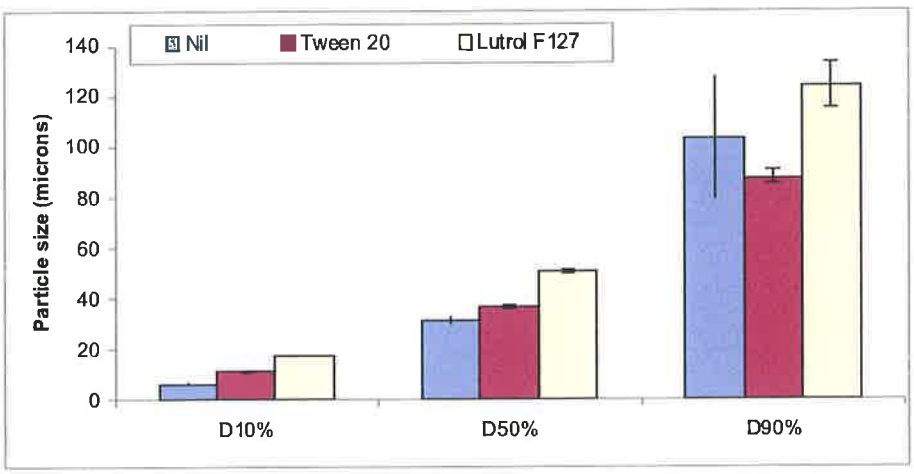


Figure 4.6: Influence of addition of plasticizer on the DFS/EC microparticle size

The effect of increase in Tinlet (°C) on the microparticle characteristics was examined for the formulation containing Tween 20. No change in particle size or product yield was observed at the higher inlet temperature (Figure 4.7).

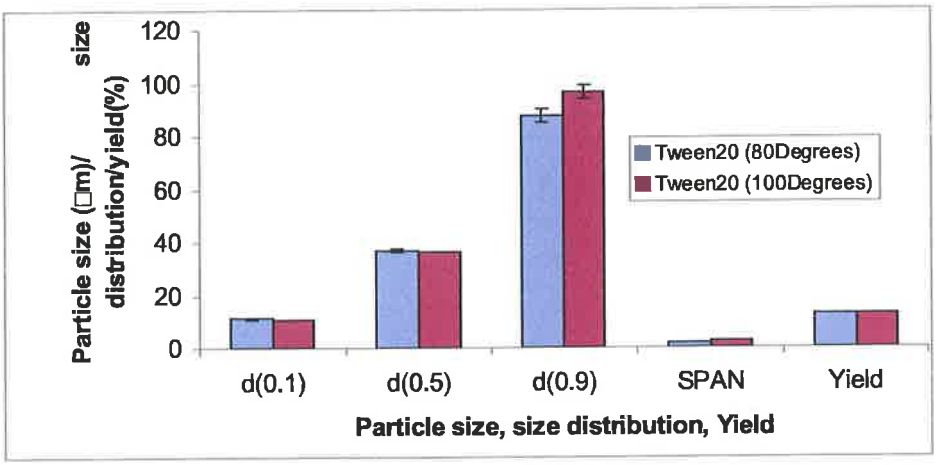


Figure 4.7: Influence of increase in spray drying inlet temperature (Tinlet) on the DFS/EC microparticle size and product yield

Electron micrographs of the microparticles showed little/no morphological differences between the batches, irrespective of the presence of plasticizer or an increase in inlet temperature from 80 to 100°C. All microparticles showed spherical morphology with smooth surface (Figure 4.8).

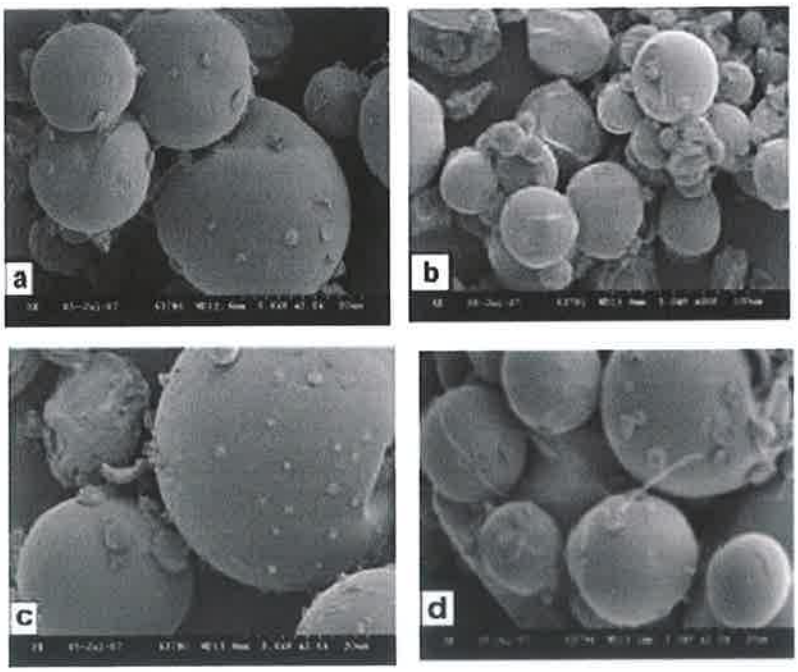


Figure 4.8: Electron micrographs of DFS/EC microparticles produced containing, (a) no plasticizer, (b) Lutrol F127, (c) Tween 20 at 80 °C and (d) Tween 20, Tinlet increased from 80 to 100°C

Little or no enhancement in flow properties was observed with the inclusion of Lutrol F127 as plasticizer. When Tween 20 was added the Carr's index value increased to 34.23%, which indicate's a decrease in rheological properties, however when the Tinlet for the batch containing Tween 20 was increased to 100°C, a significant decrease in CI value indicate's improved flowability of the microparticles (Table 4.8).

At the higher inlet temperature, evaporation of a solvent is enhanced leading to a drier product, measured by TGA (Billon et al., 2000). Rattes and Oliveira, (2007) developed SD aqueous dispersions of ethylcellulose (surelease) and eudragit microparticles from aqueous solutions using spray drying as a microencapsulation technique and reported lower product moisture content at the higher drying temperatures resulting in better rheological properties.

Table 4.8: Influence of the presence of the type of plasticizer on the density and flow character of the DFS/EC microparticles

Plasticizer used	Rheological attributes			
	ρ_b (g/cc)	ρ_t (g/cc)	CI (%)	Flow character
Nil	0.096 ± 0.0	0.138± 0.0	30.43	Poor
Lutrol F127	0.070 ± 0.0	0.097± 0.0	27.83	Poor
Tween 20	0.073 ± 0.0	0.111± 0.0	34.23	Very poor
Tween 20 @100°C	0.068 ± 0.0	0.086± 0.0	20.93	Fair

DFS encapsulation efficiency of the microparticles was high in the range of 94.56 - 107.36%, as expected for the spray dried products (Table 4.9).

Addition of the plasticizer resulted in slowing the drug release from the microparticles. A significant decrease (ANOVA; $p < 0.005$) in the initial burst drug release was observed from 53.73% for product containing no plasticizer, to 46.16% and 43.04%, for product containing Lutrol® F127 and Tween® 20, respectively. An increase in the temperature from 80 to 100°C for product containing Tween 20 led to a further decrease in initial burst release to 40.11% (Table 4.9).

The amount of drug released over 7 hours, with addition of plasticizers was found to be lower at 69.62 - 74.58%.

Table 4.9 Influence of plasticizer on the assayed drug loading (ADL) and encapsulation efficiency (EE) and initial DFS release from DFS/EC microparticles, theoretical drug loading of 25%w/w

Plasticizer	ADL (%)	EE (%)	Initial burst release @30minutes (%) of assayed DFS
Nil	24.04	96.16	53.73
Lutrol F127	23.64	94.56	46.16
Tween 20	26.68	106.72	43.04
Tween 20 (@100°C)	26.84	107.36	40.11

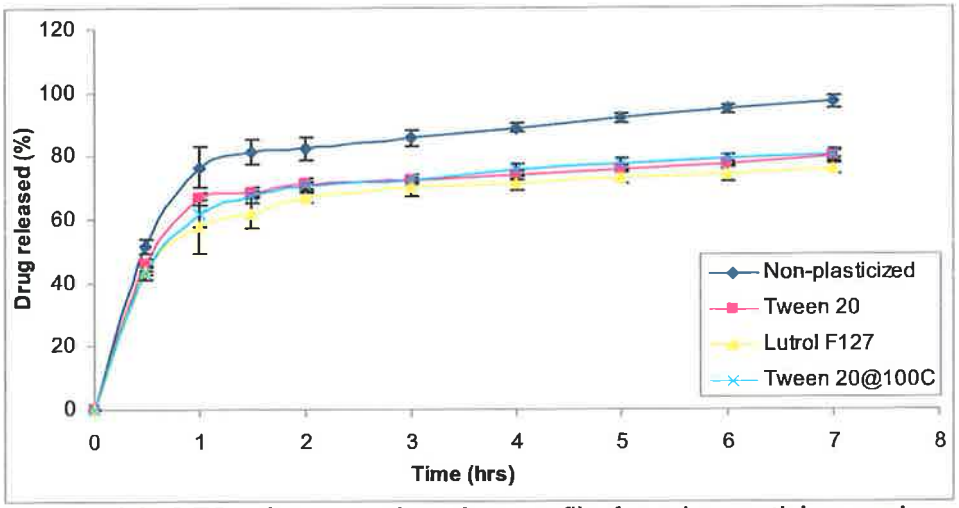


Figure 4.9: DFS release against time profile for microparticles produced without any plasticizer, and with Tween 20 or Lutrol F127

Controlled release captopril microcapsules were prepared by Singh and Robinson, (1988) using temperature induced coacervation and ethylcellulose as a controlled release polymer. Microcapsules prepared using 2%w/w Tween 80 with ethylcellulose exhibited a prolonged release where 70% of the drug was observed to be released in 55 minutes in

comparison to 7.75 minutes for control microcapsules prepared without plasticizer (surfactant).

The *in-vitro* dissolution data were fitted to the Peppas diffusion model which characterises the transport mechanism on the basis of the value of the release component "n". The value of n observed was ≤ 0.43, in the range 0.14 - 0.17, indicative that the drug release mechanism was by Fickian diffusion through the polymeric matrix

A lower release constant (k) value was observed for particles containing Lutrol® and Tween® 20, indicative of a lower initial burst release.

Table 4.10 Mathematical modeling of describing drug release from the microparticles produced at without and with the use of plasticizers

Plasticizer	Peppas model ($Q = k t^n$)		
	k	n	r^2
Nil	34.55	0.174	0.862
Lutrol F127	28.09	0.169	0.908
Tween 20	33.72	0.145	0.803
Tween 20 (@100°C)	28.14	0.179	0.877

In general, of the process and formulation parameters studied, lowering the SFR or adding the pasticizer significantly increased the particle size, lowered the bulk density and resulted in a decrease in percent yield. The morphology of the particles was enhanced at the low SFR of 350, and 300Nl/hour and at the AAR of 75%, showing smooth and spherical morphology. A decrease in FFR led to the formation of product with better rheology.

A decrease in FFR, AAR and addition of the plasticizer caused a decrease in initial burst release and a slower release of DFS over the 7 hours studied.

Two of the microparticle formulations were selected for further processing into fast disintegrating dissolving tablets (FDDTs) and were compared with tablet formulation containing the DFS API as received.

4.1.4. Formulation of diclofenac sodium FDDTs

Two of the formulations of microparticles were selected based on their sustained release profile, rheology or process yield. The RP08 batch produced at SFR of 400Nl/h, AAR and FFR of 86% and 9.6ml/min, respectively, was chosen for its relatively low initial burst release and sustained release properties and its high yield, while RP10 batch formulated at AAR of 65% was selected for its slower release profile. Though earlier RP16 batch was chosen for further optimization by addition of plasticiser, none were chosen for incorporation of FDDTs due to low spray drying percent yield of less than 30%.

Diclofenac sodium API as received and DFS/EC microparticles were formulated into selected FDDT formulations from Chapter 3, at a dose of 25mg of DFS/tablet.

FDDT formulations based on Mannitol 200 (M200) in combination with K-CLSF, Iuquasorb, SSG or SSG + calcium silicate (CaS) were selected. Magnesium stearate was added as a lubricant and raspberry or a combination of chocolate and vanilla was used as the flavours.

Placebo formulations based on M200 and the disintegrants selected showed good mechanical properties with hardness in the range 21.13 - 30.74N, friability of less than 0.66% and had fast DT in the range of 2.33 to 19.27 seconds.

The DFS containing tablets were compressed using a CF of 10kN, 15mm flat-faced, bevelled edge toolings at 7rpm and a target tablet weight of 500mg. Formulation compositions are outlined below in Table 4.11.

Table 4.11: Formulation composition for the formulation of Immediate release (IR) sustained release (SR) diclofenac sodium FDDTs

Batch no	DFS API/ SD-DFS (% w/w)	M200 (% w/w)	K-CLSF (% w/w)	L-1280 (%w/w)	SSG (%w/w) + (CaS)[+]	MgS (% w/w)
B046[*]	5[1]	85.5	5	-	-	0.5
B020[**]	5[1]	89.9	-	2	-	0.5
B012[**]	5[1]	85.4	5	-	-	2.0
B013[**]	5[1]	80.4	-	-	10	2.0
B21	5[1]	70.4	-	-	10+(10)	2.0
B014[**]	20[2]	66.9	-	-	10	0.5
B015[**]	20[3]	66.9	-	-	10	0.5
B016[**]	20[2]	71.9	5	-	-	0.5
B017[*]	20[3]	70.5	5	-	-	0.5
B019[***]	20[3]	73.9	5	-	-	0.5

[1] DFS API; [2] microparticle batch RP10; [3]RP08; [*] chocolate 4%; [**] Chocolate + Vanilla (C+V) at 2 + 0.6%w/w; [***] Raspberry 0.6%w/w; [+] only B21 contains a combination of SSG + CaS

Immediate release (IR) DFS FDDTs prepared using K-CLSF as disintegrant and chocolate as a flavour or Luquasorb® as disintegrant and chocolate and vanilla as flavours, showed sticking on the die walls accompanied with "excessive ejection force" recorded. The problem persisted even though the level of magnesium stearate (MgS) was increased to 1%w/w.

As magnesium stearate (MgS) was increased to 2%w/w, the formulation containing K-CLSF (B012) successfully resulted in the formation of tablets which had low weight variability of less than 2%. The K-CLSF tablets were porous with porosity of 27.94%, giving an average DT of 30.6 seconds. However, the formulation containing K-CLSF failed the test of friability.

FDDTs formulated using SSG (B013) or SSG + CaS (B21) with 2%w/w magnesium stearate showed no difficulty during tableting. FDDTs containing SSG had low hardness of 19.52N and a corresponding low DT

of 29.6 seconds. While FDDTs formulated using a combination of SSG and CaS had a higher hardness at 53.57N with a correspondingly higher DT of 80.4 seconds (Table 4.12a).

Even at the higher concentration of magnesium stearate (MgS) used, process-related issue of sticking and excessive ejection force recurred with tableting time, hence limiting the number of tablets formulated and impacts on the analytical testing.

Table 4.12a: Characteristics of immediate release (IR) DFS FDDTs formulated at 2%w/w magnesium stearate

Disintegrant	Weight[1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4] (%)	DT[5] (sec)	Thick[6] (mm)	Porosity (%)
K-CLSF	512.40 ± 3.47	18.38 ± 1.64	0.0207	failed[7]	30.6 ± 3.71	2.85 ± 0.01	27.94
SSG	518.80 ± 6.30	19.52 ± 2.45	0.0222	0.89	29.6 ± 1.67	2.75 ± 0.01	25.14
SSG+ CaS	517.07 ± 1.28	53.57 ± 5.20	0.0616	0.23	80.4 ± 9.91	2.60 ± 0.02	27.61

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6]Thickness [7]5 tablets broke

When the spray dried (SD) DFS/EC microparticles were used, successful production of FDDTs was observed for both batches of SD microparticles, RP10 and RP08, incorporated, even with 0.5%w/w of MgS. Formulations used contained the disintegrants, K-CLSF at 5%w/w or SSG at 10%w/w. The tablets formed had a low weight variability of less than 3% (Table 4.12b), suggesting that incorporation of either microparticle batches does not influence rheology of the tablet blend. Overall, the thickness of the tablets was found to be in the range 2.91 - 3.00mm. FDDTs formulated with K-CLSF showed higher hardness of > 38N and lower DT of below 33.6 seconds, while the hardness for FDDTs containing SSG was lower at < 25N, with the DT higher at > 1 minute.

Table 4.12b: Characteristics of modified release (MR) DFS FDDTs formulated with 0.5%w/w magnesium stearate

Batch no	Weight [1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4] (%)	DT[5] (sec)	Porosity (%)	Drug content %
B014 (RP10)	497.60 ± 6.19	21.19 ± 1.63	0.0236	failed[6]	91.8 ± 3.11	31.39	87.31 ± 1.99
B015 (RP08)	506.60 ± 2.91	24.43 ± 3.56	0.0274	0.41	75.8 ± 3.56	28.67	109.2 ± 7.16
B016 (RP10)	509.00 ± 10.65	38.93 ± 1.81	0.0435	0.39	33.6 ± 4.77	28.52	102.0 ± 1.55
B017 (RP08)	515.92 ± 15.51	39.01 ± 5.17	0.0434	0.58	32.2 ± 2.97	28.96	108.0 ± 4.87

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6]5 tablets broke

Corresponding placebo tablets containing K-CLSF showed hardness and DT values of 45.73N and 12.33 seconds, respectively. Addition of DFS API was found to decrease the hardness and increase the DT to 18.38N and 30.6 seconds, respectively. In contrast, tablets containing microparticles of DFS had relatively higher hardness values at 38.93 - 39.01N, although the DT was similar at 32.20 - 33.6 seconds.

For the SSG containing FDDTs, the placebo tablets had hardness and DT of 49.47N and 36.67 seconds, respectively. Addition of DFS API caused a decrease in hardness and DT to 19.52N and 29.6 seconds, respectively, while addition of microparticles of DFS caused a decrease in hardness to 21.19 - 24.43N, and an increase in DT to > 1 minute.

Overall, inclusion of DFS as received and the DFS microparticles resulted in the formation of softer tablets, probably due to a decrease in the binding capacity of the blend. An increase in the DT was observed which is related to the hydrophobic nature of DFS. Abbaspour et al., (2008) observed that while placebo tablets had a hardness of 8.8kg (86.30N) and a disintegration time of 5 seconds, an increase in the DT to 1 - 2 minutes was observed when pellets of Ibuprofen was added to the formulation. The

hardness of tablets was increased from 8.8 to 9.6kg. The friability was higher at 2.3 - 5.4% in contrast to our formulation. Rawas-Qalaji et al., (2006) reported that with an increase in epinephrine load from 0 to 20mg, a corresponding decrease in hardness from 12 to 2kg and a decrease in DT from 37.2 to 5.6 seconds was observed. This could be due to the hydrophilic nature of epinephrine.

4.1.4.1. Stability studies

Stability tests were carried out over 6 months, on FDDTs formulated using K-CLSF as a superdisintegrant and the DFS/EC microparticle batch RP08. Two batches were placed on stability, batch B017 which was formulated using chocolate flavour at 4%w/w and batch B019 formulated using raspberry flavour at 0.8%w/w.

Little or no change in weight and weight variability was observed over time. A weight variability of less than 3% was observed in all cases (Table 4.13).

Table 4.13: Characteristics of MR DFS FDDTs over 6 months stability at uncontrolled ambient conditions (lab temperature and humidity)

Time (month)/ batch	Weight[1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4] (%)	DT[5] (sec)	Porosity (%)	Drug content %
0/B017 (RP08)	515.92 ± 15.51	39.01 ± 5.17	0.0434	0.58	32.20 ± 2.97	28.96	108.0 ± 4.87
1	524.55 ± 7.74	31.93 ± 6.39	0.0357	0.63	26.83 ± 2.23	26.52	102.8 ± 2.82
6	521.26 ± 13.98	33.66 ± 8.11	0.0376	0.91	21.33 ± 1.86	26.98	104.0 ± 0.80
0/B019 (RP08)	512.28 ± 13.39	36.16 ± 5.66	0.0403	0.39	28.50 ± 3.31	28.77	109.3 ± 0.92
1	513.56 ± 7.18	34.50 ± 1.24	0.0386	0.41	18.00 ± 1.00	27.84	107.7 ± 1.97
6	508.55 ± 16.40	34.62 ± 9.99	0.0387	0.39	18.00 ± 3.34	28.55	100.3 ± 6.51

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6]Thickness

A non-significant decrease (ANOVA; $p > 0.05$) in hardness and a significant decrease (ANOVA; $p < 0.05$) in the DT of the FDDTs was observed with time (Figure 4.10). Overall, the DT of tablets was below 40 seconds. A decrease in FDDT drug content was also observed with time (Figure 4.10).

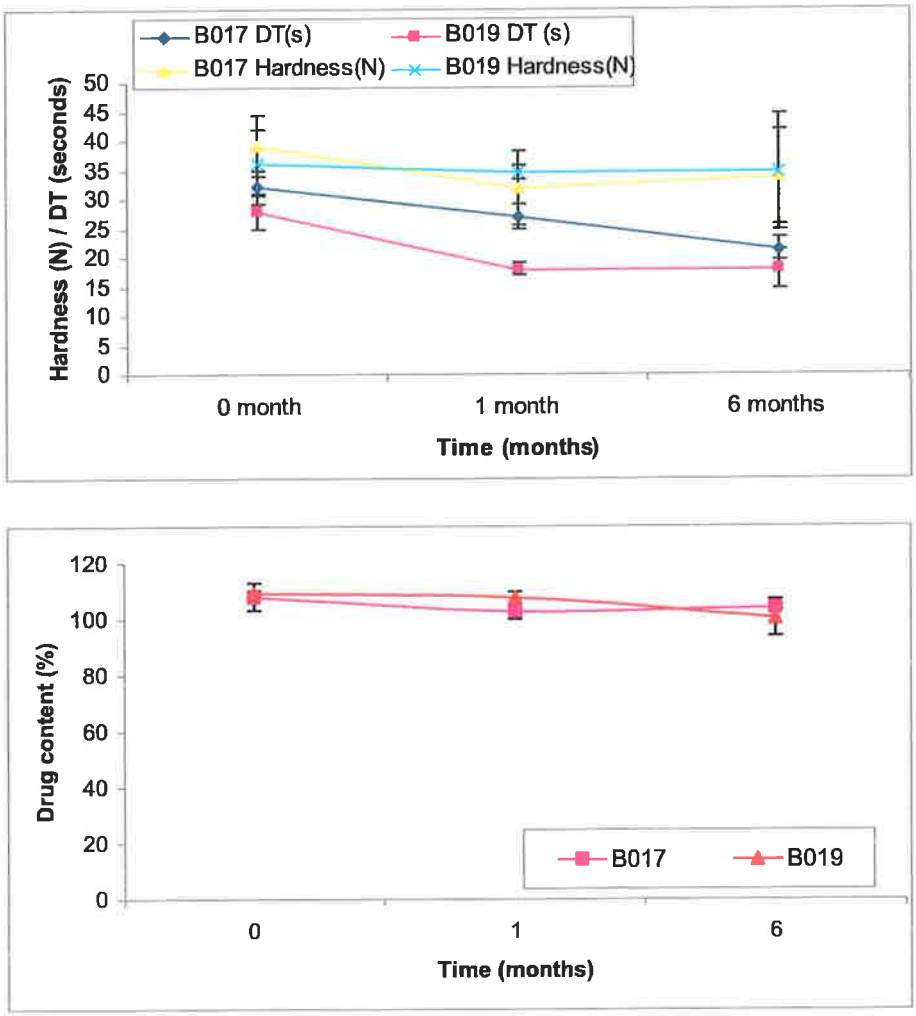


Figure 4.10: Characteristics of MR DFS FDDTs during 6 month stability

4.1.4.2. Preclinical palatability study in canine model

The palatability of the mannitol based placebo tablets and SR DFS FDDTs was evaluated in the canine model. The palatability study was carried out

in the ethically approved test facility of Charles River Laboratories Biolabs Europe (CRLBLE), Ballina, Co Mayo.

Six clinically healthy male dogs (13 to 20 months old) that met the inclusion criteria were allocated for the offering of the FDDT on study days 0, 1 and 2. All animals were offered three different formulations of the FDDT each containing different flavours on study days 0, 1 and 2. Each animal was observed for flavour preference, intake and refusal of the FDDT. The three different formulations, formulation 1, 2 and 3 studied are listed in Table 4.14. Formulations 1 and 2 were flavoured placebo tablets and there were three flavours for each formulation, *i.e.* tablets 1A, 1B, 1C and tablets 2A, 2B and 2C. Formulation 3 contained microparticles equivalent to 25 mg sodium diclofenac and had two flavours, 3A and 3B.

Table 4.14 List of investigational FDDTs studied in canine model

Formulation (Study Day)	Placebo /Active	Flavour	Batch No.
1(0)	Placebo	Chocolate (1A)	B001
	Placebo	Raspberry (1B)	B018
	Placebo	Chocolate + vanilla (1C)	B002
2(1)	Placebo	Raspberry (2A)	B020
	Placebo	Chocolate (2B)	B003
	Placebo	Chocolate + vanilla (2C)	B004
3(2)	25mgDFS/FDDT	Chocolate (3A)	B017
	25mgDFS/FDDT	Raspberry (3B)	B019

The results of the study showed that the FDDTs were palatable to the dogs (Table 4.15). On 2 of the 3 days studied, 4/6 dogs willingly took the formulations. On study day 0, three different flavours (n = 6 dogs per flavour), *i.e.* 1A, 1B or 1C of formulation 1 were offered to the animals. During the palatability test, there was variation in the response of individual animals to different flavours of formulation 1. Two animals showed first preference for flavour 1A, whereas one animal showed second preference for flavour 1A. All three animals fully consumed flavour 1A tablets after intake. Two of the animals showed first preference for flavour 1B. One

animal showed second preference for flavour 1B. Three animals completely consumed the tablets of flavour 1B after intake. One animal tasted the flavour 1B but refused it later on. Two animals had third preference for flavour 1C. One animal showed second preference for flavour 1C. All three animals completely consumed the tablets of flavour 1C after intake. Overall during the palatability test on study day 0, the flavour preference order by all animals was 1A followed by 1B and 1C (Table 4.15).

On study day 0, only four animals had successful intake of formulations within 90 seconds. This indicates that the offered flavours of formulation 1 were the most palatable to the animals that were offered them. Two animals did not show intake of any formulation which possibly indicates their disliking for the offered flavours.

On study day 1, three different flavours (n = 6 dogs per flavour), *i.e.* 2A, 2B or 2C of formulation 2 were offered to the animals. During the palatability test, there was variation in the response of individual animals to the different flavours of formulation 2. One animal showed first preference for flavour 2A. Three animals showed third preference for flavour 2A. All three animals had completely consumed the tablets of flavour 2A after intake. Overall, during the palatability test on study day 1, the preferred flavour was 2C followed by 2B and 2A. On study day 1, four out of the six animals had successful intake of formulations within 90 seconds. This indicates that the offered flavours of formulation 2 were the most palatable to the animals. Two animals did not show intake of any formulation which possibly indicates their disliking of the offered flavours.

On study day 2, two different flavours (n = 6 dogs per flavour), *i.e.* 3A or 3B of formulation 3 were offered to the animals. During the palatability test, there was variation in the response of individual animals for different flavours of formulation 3. One animal showed first preference for flavour 3A whereas three animals showed first preference for flavour 3B, three animals first tasted flavour 3B but then refused it. Overall, during the palatability test on study day 2, flavour 3A was completely consumed by

three animals and refused by one animal. Flavour 3B was completely consumed by one animal whereas it was refused by three animals. This suggests that the taste of flavour 3A was preferred to flavour 3B. On study day 2, four out of the six animals had successful intake of formulations within 90 seconds indicating the palatability of the offered flavours of formulation 3 by the animals.

Table 4.15: Flavour preference order and intake time of animals during the palatability test of different formulations of FDDT.

Study Day	Flavour	Animal No.	Intake in 90 sec	Flavour(s) preference order	Assessment score*
		68571	Yes	1A, 1B and 1C	2
	1A	79591	Yes	1B, 1A and 1C	2
0	1B	95580	Yes	1B	1
	1C	36328	Yes	1A, 1C and 1B	2
		60561	No	None	0
		11794	No	None	0
		68571	Yes	2B, 2C and 2A	2
	2A	79591	Yes	2C, 2B and 2A	2
1	2B	95580	No	None	0
	2C	36328	Yes	2C, 2B and 2A	2
		60561	Yes	2A, 2C	2 (2A); 1 (2C)
		11794	No	None	0
		68571	Yes	3B, 3A	1 (3B); 2 (3A)
		79591	Yes	3B, 3A	2
2	3A	95580	No	None	0
	3B	36328	Yes	3B, 3A	1 (3B); 2 (3A)
		60561	Yes	3A, 3B	1
		11794	No	None	0

*Score 0 - formulation refused; Score 1 - formulation tasted but refused later on; Score 2- formulation taken

During the course of the study no abnormalities were observed in general physical appearance and behaviour of the animals. No abnormalities of

food and water consumption and appearance of urine and faeces were observed throughout the study in all animals.
This demonstrates adequate taste masking of DFS by coating it with ethylcellulose using spray drying technique.

4.2. Conclusions

Spray drying of ethanolic solution of DFS/EC, containing DFS:EC at a 1:3 ratio resulted in microparticles of 11 - 31.60μm

Of the parameters examined, only SFR was found to affect particle size. With a decrease in the SFR from 400 to 300Nl/h, a significant increase in median particle size from 11.05 to 31.60μm was observed. While, Esposito et al (2000) prepared Eudragit microparticles by spray drying using a hydroalcoholic solvent and reported a decrease in median diameter from 5.04 to 6.14μm, with a decrease in SFR from 800 to 400Nl/h.

A decrease in SFR also resulted in an improvement in microparticle morphology giving spherical particles with smooth surface and enhanced flowability was observed. A decrease in the AAR also resulted in particles with spherical morphology and improved rheology. A decrease in FFR caused formation of agglomerates evident from the SEM.

A decrease in both, SFR and AAR caused a corresponding decrease in percentage yield from 59% to 26%, and 59% to 35% respectively, while, a decrease in FFR caused only a marginal decrease in the percentage yield from 59% to 50%. While, Esposito et al (2000) reported a decrease in yield from 45 to 26% and 55 to 49%, with a decrease in SFR from 800 to 400 Nl/h and AAR from 35 to 28m^3/hr. A decrease in FFR from 5 to 0.5ml/min caused an increase in yield from 38 to 48%. Therefore, it was evident that our formulation had the highest yield of 59%.

The release of DFS from the microparticles prepared was sustained over at least 7 hours with drug release controlled by Fickian diffusion.

The initial burst release from the microparticles was relatively high in the range 40 - 72%. This was expected considering the small particle size and high drug load.

zur Mühlen et al., (1998) found that tetracaine release from compritol lipid microparticles was dependent on the particle size. The initial burst release at 30 minutes decreased from 85% to 23%, as the particle size increased from less than 40μm to between 630μm - 1mm.

Gavini et al (2004) prepared PLGA microspheres of vancomycin using emulsification/spray drying. It was reported that for the microspheres of particle size 11.15 to 10.96μm, a decrease in drug loading from 33% to 25% to 20%w/w, led to a corresponding decrease in the actual drug content from 27.4% to 21.5% to 19.9%, respectively, and an increase in encapsulation efficiency from 84.2% to 86% and 99.5%, respectively. A decrease in initial burst release after 30 minutes was reported from 62% to 56% to 20%.

Addition of plasticizer resulted in a lower initial burst release of DFS from the EC microparticles, probably due to formation of tough and flexible ethylcellulose films. However, a corresponding decrease in percentage yield was also observed from 27.3% to 13% and 8.5%.

Incorporation of DFS API to the mannitol based FDDTs in combination with the superdisintegrants K-CLSF, Luquasorb® or SSG, showed tablet process related issues such as excessive sticking to tablet punches and dies and excessive tablet ejection force. This was related to the hydrophobic nature and physicochemical properties of the drug. An increase in the level of magnesium stearate from 0.5 to 2%w/w helped in the formation of tablets without sticking. While, formulation of FDDTs containing DFS microparticles did not show sticking to punch and dies.

Addition of either DFS API or DFS microparticles to the placebo tablets caused an alteration in the FDDT characteristics. Corresponding placebo tablets containing K-CLSF had hardness and DT values of 45.73N and 12.33 seconds, respectively. Addition of DFS API generated tablets of

lower hardness at 18.38N and higher DT of 30.6 seconds, while for the tablets containing microparticles of DFS, the tablets hardness was relatively higher, but lower than the placebo at 38.93 - 39.01N. The DT value of these FDDTs was highest ranging 32.20 - 33.6 seconds.

When SSG was used as the disintegrant, placebo tablets had hardness and DT of 49.47N and 36.67 seconds, respectively. Addition of DFS API caused a decrease in both hardness and DT to 19.52N and 29.6 seconds, respectively. Similarly, addition of DFS microparticles to the placebo caused a decrease in hardness to 21.19 - 24.43N, and an increase in DT to > 1 minute.

Abbaspour et al., (2008) observed that while placebo tablets had a hardness of 8.8kg and a disintegration time of 5 seconds, an increase in the DT to 1 - 2 minutes was observed when pellets of Ibuprofen was added to the formulation. The hardness of tablets was increased from 8.8 to 9.6kg. The friability was higher at 2.3 - 5.4% in contrast to our formulation.

Rawas-Qalaji et al., (2006) reported that with an increase in the drug content of the hydrophilic drug, epinephrine, from 0 to 20mg, a corresponding decrease in hardness from 12 to 2kg and DT from 37.2 to 5.6 seconds was observed.

The modified release FDDTs were found to be stable over a period of 6 months, when stored in securitainers under uncontrolled lab conditions. No significant change in tablet hardness was observed. A decrease in DT by 10 seconds was observed during the 6 month storage.

A palatability study carried out in the dog model showed that 4/6 dogs voluntarily accepted the FDDTs, suggesting good palatability of the FDDTs, probably enhanced by taste masking of the diclofenac sodium by microencapsulation.

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In the next chapter, an attempt was made to formulate fast disintegrating tablets (FDTs) of our next hydrophobic model drug, i.e. simvastatin. The influence of increasing simvastatin content on the FDT characteristics was also investigated.

CHAPTER 5

Influence of including simvastatin, a lipophilic antilipidaemic agent, on the characteristics of FDDTs formulated using a water-soluble and a water insoluble DC filler

5.0. Introduction

Simvastatin is a weak acid with a pKa of 4.18 and has a log partition coefficient in octanol/water (log P) of 4.4 (Margulis-Goshen and Magdassi, 2009). It is a white, non-hygroscopic, lipophilic drug with a low aqueous solubility, approximately 30μg/ml (O'Neil, 2006). According to the biopharmaceutics classification system (BCS), simvastatin categorized as a class II drug; of low solubility and high permeability. As for compounds with low aqueous solubility, simvastatin exhibits low and variable bioavailability associated with dissolution rate-limited absorption after oral administration. The systemic bioavailability of the simvastatin is reported to be <5% of the dose ingested (Rytting et al., 2005; Yoshinari et al., 2007).

The aim of this study was to examine the effect of including simvastatin, a lipophilic drug, on the characteristics of FDDTs formulated using the water-soluble DC filler, Mannitol 200 and the water insoluble DC filler, cellulose based Prosolv® HD90. Unlike conventional tablets, which are swallowed and subsequently disintegrate in the GIT in 15-30 minutes, fast disintegrating dissolving tablets (FDDTs) are designed to disintegrate/melt in mouth, ideally within less than a minute. Therefore simvastatin will be expected to be released relatively faster from the FDDT tablet matrix in comparison to the commercially available conventional simvastatin tablets, giving higher and less variable bioavailability of the drug. In addition, formulating simvastatin as FDDTs would also have the advantage of offering an easier dosage form and may lead to better patient compliance.

To date there are no fast dissolving disintegrating tablets (FDDTs) containing simvastatin on the market.

Preformulation characterisation of simvastatin and its compatibility with the excipients selected for its formulation into FDDTs were first carried out and are discussed below.

5.1. Preformulation studies on simvastatin API

Preformulation characterisation of simvastatin API was carried out prior to formulation of simvastatin FDDTs. The tests conducted included particle size analysis, density and rheology measurements. Thermal analysis; DSC and TGA was carried out on simvastatin and its combination with tableting excipients.

Simvastatin was analysed for particle size by dry method using Malvern Mastersizer 2000, as per the method outlined in section 2.1.5.1, Chapter 2. The median particle size (D50%) of simvastatin API was found to be 7.39µm. The particle size distribution showed a bimodal size distribution, with a second distribution below 2µm related to the presence of fines in the API (Figure 5.1).

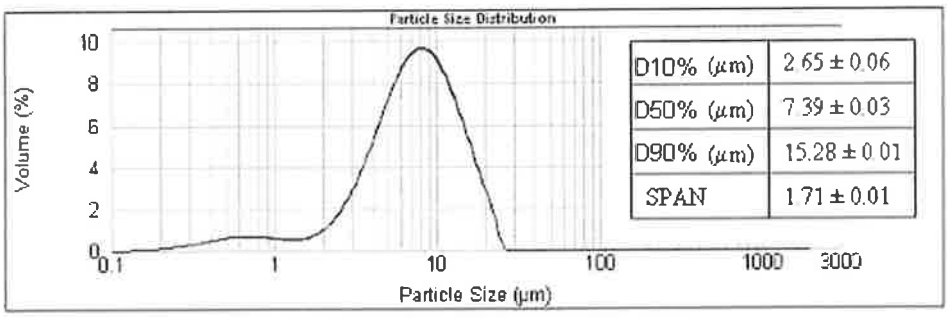

Figure 5.1: Particle size distribution of simvastatin API

The bulk and tapped density of simvastatin API, carried out as detailed in section 2.1.5.3, Chapter 2, were found to be 0.2169 ± 0.02 g/cc and 0.2629 ± 0.02 g/cc, respectively. The Carr's compressibility index derived from the calculated values of bulk and tapped density values was found to be 17.46%, which, according to the scale of flowability (BP 2008), corresponds to a 'fair' flow.

The flow property was also measured using the angle of repose. The angle of repose value for the simvastatin API of 52.70°, corresponds to poor flow property. This occurrence was expected due to the median particle size of 7.39µm obtained for simvastatin and possibly as a result of the hydrophobic property of simvastatin (Table 5.1).

Table 5.1 Flow property measurement of simvastatin API

Test	Result	Flow character
Carrs index[a] (%)	17.46 ± 2.57	Fair
Angle of repose[b] (°)	52.70 ± 0.19	Poor (must agitate, vibrate)

The electron micrograph of simvastatin revealed elongated crystals (Figure 5.2), similar to the crystal morphology previously reported by Jun et al (2007). The elongated crystals explain the poor flow property of simvastatin as measured by the angle of repose.

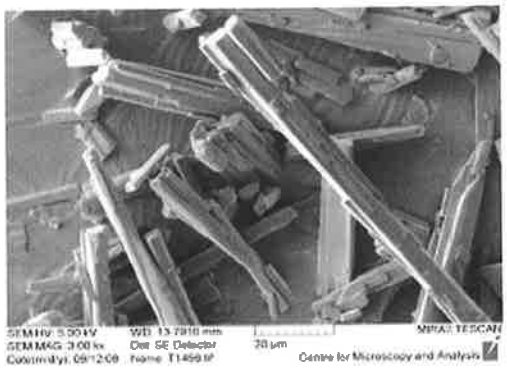

Figure 5.2: Electron micrograph showing the morphology of simvastatin API

DSC studies on simvastatin API showed a single sharp endothermic peak corresponding to the melting point of simvastatin API at 140.01°C (Figure 5.3), which is close to the literature value of 139.5°C (Jun et al., 2007). This confirms the crystalline nature of simvastatin API.

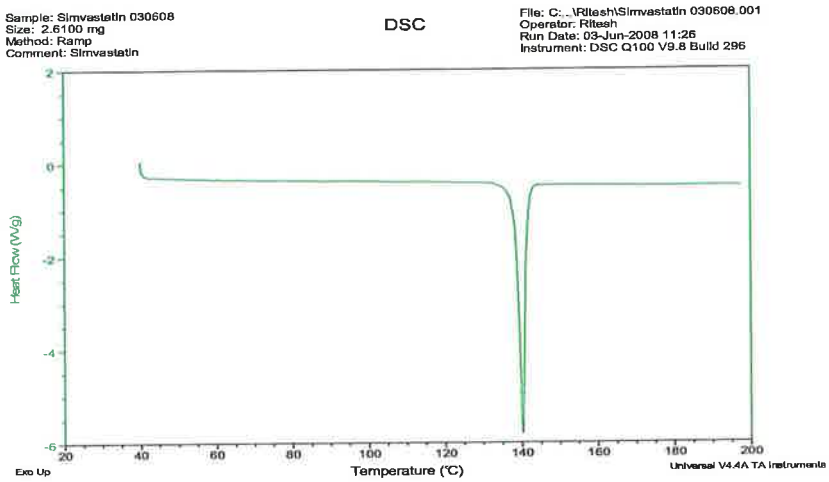

Figure 5.3: DSC thermogram for simvastatin API

TGA conducted on simvastatin API showed a negligible percentage weight loss of 0.029% in the temperature range 0 - 150°C (Figure 5.4). This indicates that simvastatin was in a relatively dry form probably due to its non-hygroscopic nature. After 210°C a gradual loss in weight was observed probably due to degradation of simvastatin. Souza et al., (2007) observed a similar phenomenon during the TGA analysis in nitrogen after a temperature of 203°C.

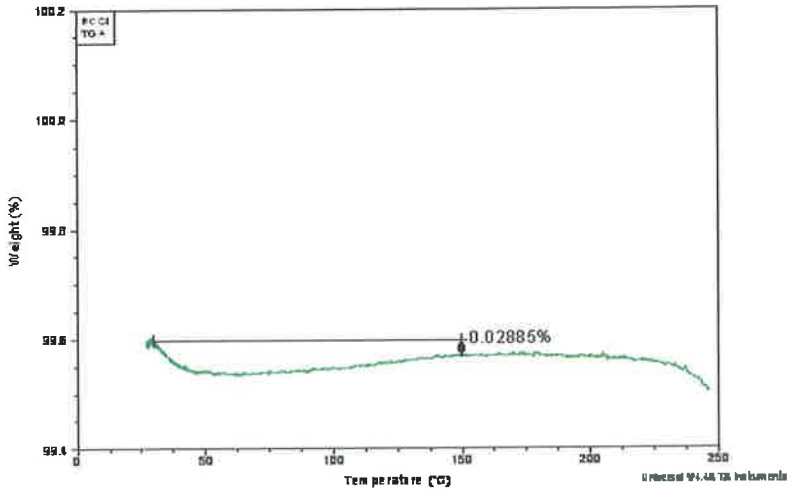

Figure 5.4: TGA trace of simvastatin API

5.2. Drug - excipient compatibility studies using DSC

DSC studies were carried out on the individual component and physical mix (PM) of simvastatin with a number of tableting excipients (in approximate weight ratio of 1:1), selected to be incorporated into simvastatin FDDT formulations. DSC thermograms of individual components, i.e. filler M200, superdisintegrant K-CLSF and lubricant, magnesium stearate and their corresponding physical mixtures with simvastatin are illustrated in Figure 5.5. The peak temperature and associated enthalpy of all the events is presented in Table 5.2. No new thermal events were noted for any of the physical mixture. DSC profiles for each mix showed endothermic transition representative of the individual components. A small deviation in the melting point of each component for the physical mix can be due to the presence of mixed composition.

DSC thermogram of simvastatin only showed a peak melting temperature of 140.01°C and an ΔH_{fus} 59.53J/g (Figure 5.5a). DSC of M200 displayed a melting endothermic event at 168.39°C (ΔH_{fus} 319J/g) that was consistent with the literature (Cavatur et al 2002), whereas the physical mix of M200 (1.27mg) and simvastatin (1.02mg) showed two endothermic events, (1) at 139.82°C (ΔH_{fus} 29.35J/g) representative of the simvastatin component and (2) a second event at 166.47°C (ΔH_{fus} 145.8J/g) representative of the M200 component (Table 5.2). The ΔH_{fus} of each component did not indicate any interaction between the drug and filler. Similarly, DSC thermograms of K-CLSF and simvastatin at the ratio of 0.80mg:0.98mg were representative of each component and did not indicate any interaction between the simvastatin and K-CLSF.

DSC thermograms of magnesium stearate (MgS) displayed two different endotherms, at 89.87°C (ΔH_{fus} 67.12J/g) and at 116.31°C (ΔH_{fus} 122.3J/g). The first event can be attributed to the dehydration of the magnesium stearate, and the second transition can be assigned to the melting endotherm of MgS (Sharpe et al 1997). A physical mix of simvastatin and magnesium stearate (0.44mg) showed three thermal events at 94.83°C

(ΔH_{fus} 1.693J/g) and at 101.82°C (ΔH_{fus} 18.25J/g) related to MgS and a third endotherm indicative of melting of simvastatin at 139.10°C (0.45mg, ΔH_{fus} 8.969J/g). The shift in thermal events of magnesium stearate may indicate a possible interaction with simvastatin. However, MgS is only used at a small percent of the tablet blend formulation at 0.5 to 2%w/w, while the change observed here is at a 50%w/w composition.

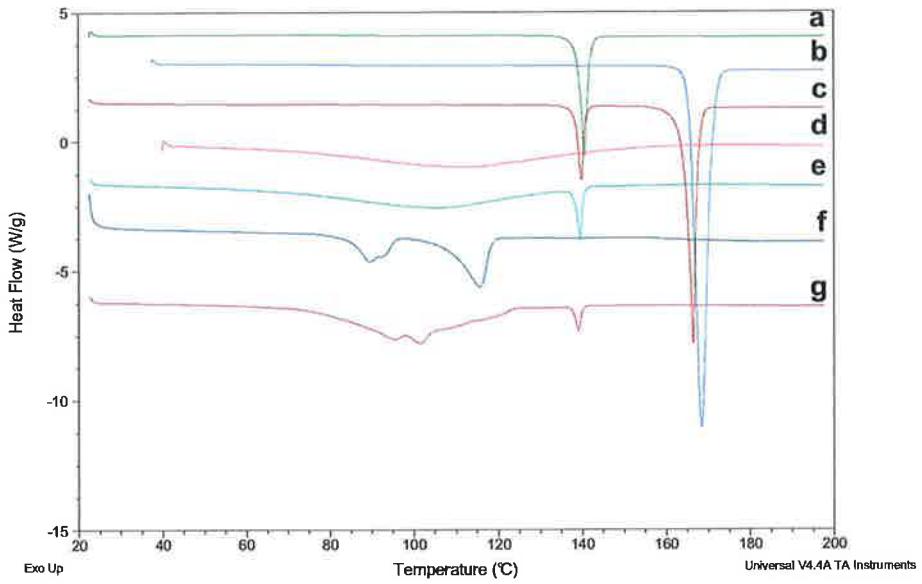

Figure 5.5: DSC thermograms of pure components (a) simvastatin, (b) M200, (d) K-CLSF, (f) MgS and physical mixture of simvastatin with (c) M200, (e) K-CLSF, (g) MgS

Table 5.2: DSC data of pure components and physical mixtures of simvastatin, MgS, K-CLSF and M200

Excipient/ drug-excipient physical mixture	Literature value (°C)	Peak temp. (°C)	Enthalpy of fusion ΔH_{fus} (J/g)
Simvastatin (SIM)	139.5	140.01	59.53
Mannitol 200 (M200)	165.0	168.39	319.0
Physical mix: SIM+M200	-	139.82	29.35
	-	166.47	145.8
Kollidon CLSF (K-CLSF)		111.57	255.4
Physical mix: SIM+K-CLSF	-	105.47	134.0
	-	139.51	17.89
Magnesium stearate (MgS)	92.3	89.87	67.12
	115.0	116.31	122.3
Physical mix: SIM+MgS	-	94.83	1.693
	-	101.82	18.25
	-	139.10	8.969

Hence it can be concluded that simvastatin does not interact with the major tableting excipients used in the present study for the formulation of FDDTs.

5.3. Formulation and characterisation of simvastatin FDDTs

Based on the FDDT formulations developed in chapter 3, the influence of adding simvastatin in selected formulations of M200 and Prosolv® on the characteristics of the tablets was evaluated. The disintegrants selected were K-CLSF, Luquasorb®, SSG and a combination of SSG and calcium silicate (CaS).

When placebo FDDTs were previously formulated using M200 or Prosolv® with the superdisintegrant K-CLSF, favourable mechanical properties; hardness of 30.74 ± 1.08N and 96.98 ± 2.91N, respectively and low disintegration times of 15.67 ± 1.53 seconds and 11 ± 5.57 seconds,

respectively were observed (Table 3.7, chapter 3). In chapter 4, when DFS API was formulated in an FDDT blend of M200 and K-CLSF, the FDDTs showed an increase in DT at 30.6 seconds, while addition of microparticles of DFS in the same formulation composition showed an increase in DT at 33.6 seconds.

When M200 was used in combination with Luquasorb® to formulate placebo FDDTs (Chapter 3), the FDDTs showed a very low DT of 2.33 ± 0.58 seconds, the lowest DT achieved using a direct compression tableting process. The FDDTs also showed a reasonable hardness of 21.13 ± 2.48N. Interestingly when Luquasorb® was used with Prosolv®, the FDDTs showed a high hardness value of 119.55 ± 6.98N and a relatively high disintegration time of 47.67 ± 3.06 seconds (Table 3.7, chapter 3). In this study, Luquasorb® was used as a disintegrant with M200 only.

The third disintegrant, SSG, when formulated with either M200 or prosolv previously was shown to give FDDTs with hardness of 28.89 ± 6.45N and 141.11 ± 20.42N respectively and low DT of 19.67 ± 2.52 and 7.33 ± 0.58 seconds, respectively; (Table 3.7, chapter 3). In chapter 4 when DFS API was formulated in an FDDT blend of M200 and SSG, the FDDTs formulated showed a longer DT at 29.6 seconds, while microparticles of DFS in the same formulation showed an increase in DT at > 75 seconds. In the present study, only Prosolv® was selected for evaluation in combination with SSG.

Both, M200 or prosolv when used in conjunction with a combination of disintegrant (SSG) and dispersing agent (CaS), generated placebo tablets with favourable characteristics, hardness of 29.78 ± 0.81N and 76.91 ± 1.96N respectively and DT of 17.67 ± 2.08 seconds and 5.33 ± 1.15 seconds respectively (chapter 3, Table 3.7). When DFS API was formulated into FDDTs using M200 with a combination of SSG and CaS, tablets showed an increase in DT at 80.4 ± 9.91 seconds (Table 4.12, chapter 4). In the present study, the combination of SSG and CaS as

disintegrants was used with the filler Prosolv® to formulate simvastatin FDDTs.

5.3.1. Simvastatin FDDTs based on Mannitol 200

Mannitol 200 (M200) was used in combination with K-CLSF or Luquasorb® to formulate FDDTs containing simvastatin. The simvastatin content of the FDDTs was maintained at 0, 5%w/w and 10%w/w loading corresponding to a simvastatin dose of 0 - 20mg/tablet, at tablet weights of 200mg using 10mm FBE tablets. A higher dose of simvastatin of 30mg per 300mg tablet weight (10%w/w) was formulated using 13mm FBE toolings. Formulation and process parameters of the various batches of simvastatin FDDTs studied using M200 as filler are shown in Table 5.3. Details of the formulation composition of the simvastatin batches is given in Appendix 3, Table 1 and 2.

The FDDTs were compressed using 10kN compression force. A lower compression force of 7kN was used for Luquasorb® tablets due to sticking issues encountered while preparing simvastatin FDDTs (data not shown). The batches were compressed with or without flavours and magnesium stearate was added at 0.5%w/w as lubricant.

The flavours used were either, vanilla and chocolate (VC) or raspberry and mint (RM).

Table 5.3 Formulation and process parameters of round FBE simvastatin FDDTs formulated using Mannitol 200 as filler.

Batch no	Active loading/tablet	Filler used	Flavour	Tooling	Weight
B036	Placebo	K-CLSF	N/A	10 mm	200mg
B040	10mg; 20mg	K-CLSF	N/A	10 mm	200mg
B041					
B029	Placebo	K-CLSF	VC[1]	10 mm	200mg
B042;	10mg	K-CLSF	VC[1]	10 mm	200mg
B043	20mg				
B030	Placebo	K-CLSF	RM[2]	10 mm	200mg
B044;	10mg	K-CLSF	RM[2]	10 mm	200mg
B045	20mg				
B071	Placebo	K-CLSF	CM[3]	13 mm	300mg
B073	30mg	K-CLSF	CM[3]	13 mm	300mg
B072	Placebo	K-CLSF	RM	13 mm	300mg
B074	30mg	K-CLSF	RM	13 mm	300mg
B034	Placebo	Luquasorb	VC	10 mm	200mg
B046;	10mg	Luquasorb	VC	10 mm	200mg
B047	20mg				
B035	Placebo	Luquasorb	RM	10 mm	200mg
B048;	10mg	Luquasorb	RM	10 mm	200mg
B049	20mg				
B077,	30mg	Luquasorb	CM	13 mm	300mg
B083	30mg				

[1]VC - vanilla + chocolate flavour, [2]RM - raspberry + mint; [3]CM - chocolate + mint

The characteristics of the FDDTs formulated are given in Table 5.4 for K-CLSF FDDTs and Table 5.5 for Luquasorb® FDDTs. The data show that tablets produced were uniform in weight with low variability of less than 3.06%, suggesting good flowability of the tablet blends. Tablets formulated showed an increase in weight variation with increase in dose of

simvastatin. The thickness of the tablets was found to be in the range 2.33 - 2.45mm for K-CLSF tablets and 2.36 to 2.44mm for Luquasorb® tablets.

Increasing the simvastatin drug load from 0% to 10%w/w did not significantly affect ($p > 0.05$) the hardness of the tablets which was in the range 46.19 - 48.82N and 27.16 to 30.2N, for K-CLSF and luquasorb containing FDDTs respectively, except for the batch B043 where a decrease in hardness to 34.79N was observed. The percent weight loss during the friability test was less than 1% in all cases.

A significant increase in the DT of unflavoured K-CLSF FDDTs from 12 to 20.3 and 22 seconds (ANOVA, $p < 0.05$) was observed when simvastatin load was increased from 0 to 10 to 20mg. This can be due to a marginal decrease in the porosity of the tablets from 21.68 to 19.39% and the presence of the hydrophobic drug, simvastatin. An increase in DT from 12 to 17 seconds was observed for placebo FDDTs containing VC flavour although addition of simvastatin to these FDDTs did not result in a significant change in DT (ANOVA; $p > 0.05$) (Figure 5.6a).

For FDDTs containing luquasorb, when simvastatin content was increased from 0 to 5 to 10%w/w, an increase in the DT of tablets was observed; for VC flavoured tablets the DT increased from 9.6 to 28.7 to 35.7 seconds, and for RM flavoured tablets the DT increased from 9 to 30.0 and to 33.1 seconds. This was related to the decrease in porosity observed on addition of simvastatin (Table 5.5 and Figure 5.6b).

Overall, the Luquasorb® based simvastatin FDDTs had relatively lower hardness in the range 26 - 30.20N and higher DT of 28.7 - 35.7 seconds than corresponding simvastatin FDDTs containing K-CLSF as a disintegrant. The porosity of the Luquasorb® FDDTs was higher than the porosity of the corresponding M200 FDDTs which may be related to the lower compression force used for the Luquasorb® containing tablets. It was noted however that the thickness of the tablets were similar irrespective of disintegrant or CF used.

Table 5.4: Influence of increasing simvastatin load on the characteristics of 10mm simvastatin M200 FDDTs containing K-CLSF as disintegrant

SIM dose	Flavour	Weight[1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4]	DT[5] (sec)	Porosity (%)
0	Nil (B036)	197.86± 1.25	48.82± 0.81	0.1384	0.00	12.0± 2.0	21.68
10mg	Nil (B040)	203.44± 1.78	54.19± 3.07	0.1638	0.48	22.0± 2.7	19.39
20mg	Nil (B041)	201.57± 4.62	46.19± 3.56	0.1397	0.00	20.3± 4.0	19.13
0	VC (B029)	200.92± 0.82	48.16± 0.77	0.1366	0.00	17.0± 4.4	20.84
10mg	VC (B042)	201.76± 2.57	46.2± 2.07	0.1393	0.49	17.3± 4.2	20.62
20mg	VC (B043)	200.11± 6.13	34.79± 1.44	0.1050	0.90	17.0± 2.7	19.51

Table 5.5: Influence of increasing simvastatin dose on the characteristics of 10mm simvastatin M200 FDDTs containing Luquasorb® as disintegrant

SIM dose	Flavour	Weight[1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4]	DT[5] (sec)	Porosity (%)
0	VC (B034)	207.13± 0.57	27.16 ± 4.58	0.0742	0.94	9.60 ± 2.52	25.78
10mg	VC (B046)	200.27± 1.06	28.83 ± 1.25	0.0868	0.00	28.7 ± 10.3	22.18
20mg	VC (B047)	201.35± 0.97	30.20 ± 2.23	0.0902	0.50	35.7 ± 4.04	22.65
0	RM (B035)	199.47± 1.62	26.38 ± 2.34	0.0739	0.00	9.00 ± 4.00	24.26
10mg	RM (B048)	199.27± 4.82	30.44 ± 2.80	0.0918	0.98	30.0 ± 11.1	22.01
20mg	RM (B049)	205.92± 0.59	30.20 ± 2.37	0.0898	0.49	33.1 ± 7.1	21.78

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time

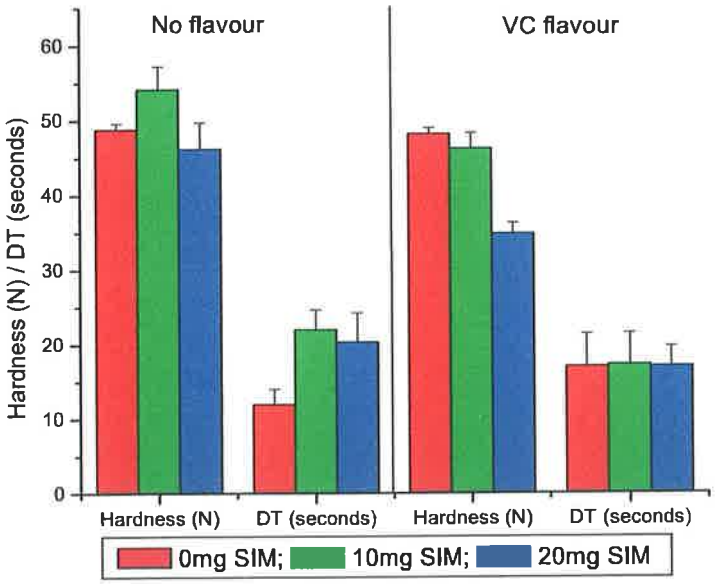

Figure 5.6a Influence of increasing simvastatin content on the hardness and DT of mannitol based FDDTs prepared using K-CLSF as disintegrant

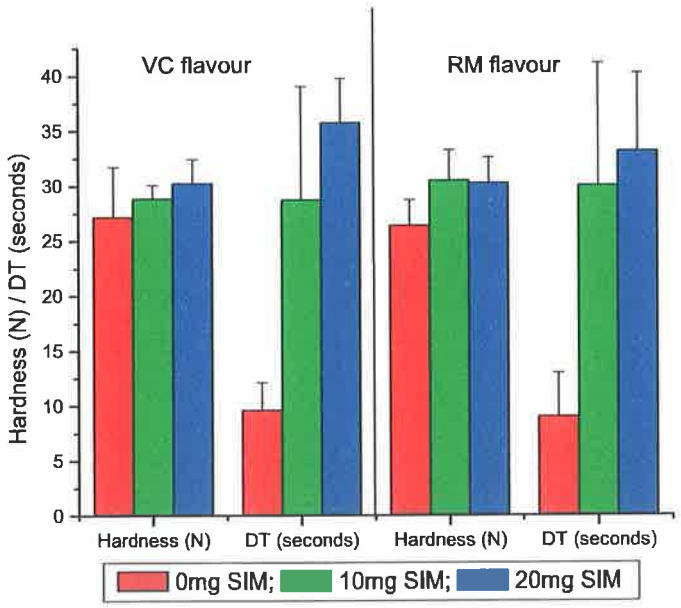

Figure 5.6b Influence of increasing simvastatin loading on the hardness and DT of mannitol based FDDTs prepared using Luquasorb® as disintegrant

Yang et al., (2004) reported an increase in the DT of the fast disintegrating tablets formulated with the hydrophobic drug, ketoprofen. The authors related this increase in DT to an increase in the wetting time of tablets and thus due to the hydrophobic nature of the drug. This is similar to our findings for simvastatin which is a hydrophobic drug, when Luquasorb® was used as disintegrant. Wettability can be measured by contact angle.
Rawas-Qalaji et al., (2006), formulated fast disintegrating sublingual tablets by direct compression using a hydrophilic model drug, epinephrine bitartrate. A range of compression force was used with 11/32-inch die and a flat, scored face, bevel-edge toolings. At the CF of 23.5kN, an increase in drug loading from 0 to 24% caused a decrease in hardness from 7.2 to 1.2N and a decrease in DT from 8 to 4.6 seconds.

FDDTs containing 10%w/w or 30mg dose of simvastatin per 300mg tablets, in combination with K-CLSF or Luquasorb® were compressed at 10kN. The flavours used were either, chocolate and mint (CM) or raspberry and mint (RM). Tablets produced were uniform in weight with variability of less than 2.17% (Table 5.6 and Table 5.7) and tablets had a thickness in the range of 2.21 to 2.32mm for K-CLSF based tablets, and 2.16 to 2.23 mm for Luquasorb® based tablets.

For tablets containing K-CLSF, the higher dose of 30mg simvastatin did not cause a change in the DT and was low in the range of 15.7 -18 seconds. In contrast, tablets containing Luquasorb® had an increase in DT from 2.3 to 26.0 seconds. Placebo (0mg simvastatin) tablets containing luquasorb had a very low DT of 2.3 seconds associated with the high porosity of these FDDTs, which decreased on addition of 30mg of simvastatin.

Except for the two batches of FDDTs that were formulated without flavour, the tablets failed friability. This was related to the low hardness of the tablets and possibly the lower thickness:diameter ratio of the 13mm tablets compared with the 10mm tablets. Also could be due to higher amount of hydrophobic (log P = 4) simvastatin.

Table 5.6: Characteristics of 30mg simvastatin FDDTs formulated using K-CLSF as disintegrant and M200 as filler

SIM dose (mg)	Flavour	Weight[1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4]	DT[5] (sec)	Porosity (%)
0*	Nil (B057)	304.77 ± 0.64	30.74 ± 1.08	0.0601	0.33	15.7± 1.53	25.84
0	CM (B071)	303.30 ± 0.94	26.26 ± 0.27	0.0516	failed[6]	17.7± 2.08	21.92
30mg	CM (B073)	299.80 ± 6.51	24.77 ± 7.43	0.0476	failed[6]	16.3± 0.58	20.63
0	RM (B072)	305.76 ± 2.87	27.28 ± 1.29	0.0532	failed[7]	17.3± 3.06	24.18
30mg	RM (B074)	302.65 ± 5.52	24.94 ± 6.26	0.0483	failed[8]	18.0± 1.00	22.98

[6]2 tablets broke during friability test; [7]4 tablets broke during friability; [8]5 tablets broke during friability test; *without flavour, taken from Chapter 3, Table 3.7.

Table 5.7: Characteristics of 30mg simvastatin FDDTs formulated using luquasorb as disintegrant and M200 as filler

SIM dose	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (sec)	Porosity (%)
0*	299.55 ± 4.28	21.13 ± 2.48	0.0414	0.66	02.3± 0.58	27.50
0** (B082)	300.99 ± 4.33	19.99 ± 0.27	0.0395	failed[6]	17.3± 1.53	21.43
30mg (B083)	303.06 ± 3.28	21.36 ± 0.99	0.0418	failed[7]	26.0 ± 5.29	21.85

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, [6]one tablet broke; [7]6 tablets broke *without flavour, taken from Table 3.7, chapter 3, **with flavour Chocolate + Mint (CM).

Assay of the simvastatin content of the FDDTs formulated showed the simvastatin content to be in the range of 93.57 to 107.6% of the theoretical drug content or label claim (Table 5.8) and were within the BP

recommended range of 90 - 110% of the label claim. This can be related to the blend uniformity and good flowability of the mannitol based simvastatin blend. Interestingly, the simvastatin content assayed for the marketed Zocor® tablets showed a high simvastatin content of >100% at 107.0-107.7% for each of the strength analysed.

Table 5.8: Assayed simvastatin content of Mannitol 200 based FDDTs

Disintegrant	Batch number	Sim dose (mg)	Assayed drug content (mg)	Assayed drug content (%)
K-CLSF	B040	10mg	09.75 ± 0.46	97.50 ± 4.11
	B042	10mg	09.48 ± 0.31	94.80 ± 2.79
	B044	10mg	09.59 ± 0.21	95.90 ± 2.29
N/A	Zocor®	10mg	10.73 ± 0.04	107.3 ± 1.77
K-CLSF	B041	20mg	19.92 ± 0.66	99.60 ± 2.80
	B043	20mg	19.11 ± 1.17	95.55 ± 3.41
	B045	20mg	19.83 ± 0.95	99.15 ± 3.71
N/A	Zocor®	20mg	21.53 ± 0.07	107.7 ± 1.13
K-CLSF	B073	30mg	28.52 ± 0.61	95.07 ± 1.46
	B074	30mg	28.07 ± 0.64	93.57 ± 1.95
N/A	Zocor®	80mg	85.61 ± 1.85	107.0 ± 2.52
Iuquasorb	B046	10mg	09.47 ± 0.35	94.70 ± 1.80
	B048	10mg	09.40 ± 0.29	94.00 ± 2.41
	B047	20mg	18.83 ± 0.48	94.15 ± 2.01
	B049	20mg	18.93 ± 1.28	94.65 ± 5.66
	B083	30mg	30.91 ± 0.48	103.0 ± 1.72

* actual simvastatin content was based on average weight of the tablets

5.3.2. Simvastatin FDDTs based on Prosolv SMCC HD 90

Simvastatin FDDTs were formulated using Prosolv® SMCC HD90 (prosolv) as the filler, at 13mm FBE, to contain simvastatin at a dose of 20mg/300mg tablets, compressed at 10kN. The disintegrants used were K-CLSF, SSG or a combination of SSG and calcium silicate. The flavour,

combination of raspberry (0.9%w/w) and vanilla cream (0.8%w/w) was used in all formulations.

All FDDTs demonstrated acceptable weight variation of less than 1% (Table 5.9). In comparison to the placebo FDDTs, the inclusion of 30mg simvastatin caused an increase in hardness for K-CLSF tablets and a decrease in hardness for SSG and SSG + CaS containing tablets. The hardness and tensile strength was highest for placebo FDDTs containing SSG, while for FDDTs containing 30mg simvastatin, FDDTs containing the disintegrant K-CLSF showed the highest hardness.

Simvastatin FDDTs formulated using Prosolv® as filler had higher hardness and tensile strength than corresponding mannitol based simvastatin FDDTs. Similar observations were made for the placebo tablets in Table 3.7, Chapter 3.

Unlike the 13mm M200 tablets, the percent weight loss during the friability test was found to be less than 0.2% and no tablets broke during friability testing. Interestingly, the Prosolv® FDDTs had a lower thickness than corresponding M200 FDDTs. The placebo Prosolv® FDDTs had a thickness in the range 2.01 - 2.08mm, while the thickness of simvastatin Prosolv® tablets were in the range 1.99 to 2.03mm.

The inclusion of 30mg simvastatin caused no significant ($p > 0.05$) impact on the DT of the tablets, which was in the range 8 - 11 seconds (Table 5.9 and Figure 5.7). DT of the M200 based simvastatin FDDTs was found to be higher and in the range 15.7 - 18.0 seconds.

Table 5.9: Influence of various superdisintegrants on the characteristics of simvastatin containing prosolv based FDDTs of 13mm diameter

Disintegrant (Sim dose)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (sec)	Porosity (%)
K-CLSF (Placebo*)	299.67 ± 2.68	96.98 ± 2.91	0.1958	0.00	11.00 ±5.57	20.02
K-CLSF (20mg)	297.70 ± 0.71	109.95 ± 11.99	0.2195	0.10	9.30 ±0.58	21.42
SSG (Placebo**)	299.18 ± 0.59	141.11 ± 20.42	0.2824	0.00	7.30 ±0.58	25.48
SSG (20mg)	295.87 ± 2.76	72.28 ± 3.57	0.1458	0.20	8.00 ±2.00	18.99
SSG + CaS (Placebo**)	302.24 ± 0.20	76.91± 1.96	0.1549	0.00	5.30 ±1.15	25.23
SSG + CaS (20mg)	306.53 ± 2.27	75.32 ± 4.27	0.1513	0.16	8.30 ±1.53	23.18

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, *Data from Chapter 3, ** Data from Chapter 3

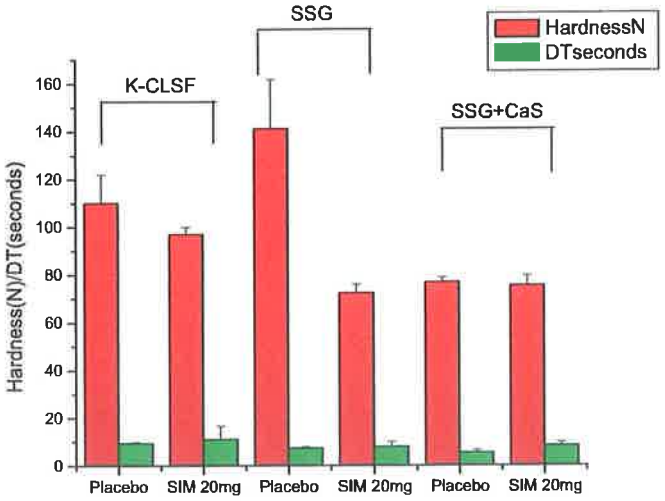

Figure 5.7 Influence of type of superdisintegrants on hardness and DT of simvastatin containing prosolv FDDTs

The assayed drug content of the simvastatin prosolv FDDTs showed a simvastatin content of >100% for FDDTs formulated using K-CLSF and mixture of SSG and CaS. A lower content of 90.60% was observed for the FDDTs formulated using SSG as disintegrant (Table 5.10).

Table 5.10: Assayed simvastatin content of prosolv FDDTs at 13mm tablet diameter

Batch number	SIM dose(mg)	Assayed drug content (mg)	Assayed drug content (%)
B117	20mg	20.01 ± 0.65	100.05 ± 3.41
B118	20mg	17.69 ± 0.39	90.60 ± 1.10
B119	20mg	21.49 ± 0.68	107.45 ± 2.77

Unlike for DFS API, the addition of simvastatin API to selected formulations from chapter 3 did not show evidence of sticking during compression or excessive ejection force. This may be related to the differences in hydrophobicity of the 2 APIs studied and/or the physical characteristics of particle size and morphology of the 2 APIs. At an industrial scale, tablets are manufactured at a relatively high speed. The formulations studied so far were compressed at the lowest speed of the tablet press used ie at 7rpm. Selected formulations were compressed at increasing compression speed from 7 to 49rpm and are described in the next section.

5.4. Influence of increase in tablet turret speed on characteristics of simvastatin FDDTs

Selected formulations containing 5%w/w or 10mg of simvastatin/200mg tablet weight were prepared using 10mm FBE tools and formulations containing 6.67%w/w or 20mg of simvastatin/300mg tablet were formulated using 13mm FBE tools. The CF used was 10kN and tableting

was carried out at three increasing turret speeds of 7rpm, 28rpm and 49rpm. Mannitol 200 was used in combination with K-CLSF and magnesium stearate. The characteristics of the simvastatin tablets formulated are given in Table 5.11. At both simvastatin content of 10mg and 20mg, as the compressional speeds was increased 4-fold and 7-fold of the original tableting speed of 7rpm, a significant increase (ANOVA; $p < 0.001$) in the weight variation was observed with maximum variability of ±10%.

For the 10mg dose in 10mm tablets, the weight variability increased from 0.83 to 2.22 and 10.04% as tablet speed was increased from 7 to 28 and 49rpm. Similarly, for the 20mg dose the weight variability increased from 0.88 to 1.23 and 5.51%. With an increase in tableting speed, variability in the tablet weight was higher for smaller diameter tablets. This increase in weight variability may be related to irregular flow of the blend at increased compression speed leading to variability in filling of the dies. This was probably a result of addition of simvastatin to the blend.

Previously in our lab, we demonstrated that an increase in tablet turret speed from 7 to 28 to 49rpm did not result in significant variation in the average tablet weight, hardness and tensile strength, tablet thickness, porosity or the DT of the FDDTs. All FDDTs passed friability studies. The formulation studied was a placebo blend of Mannitol 200, Kollidon CLSF and magnesium stearate and the compression force used was 10kN using FBE toolings of 10mm. This was related to the good rheology of Mannitol 200 as filler.

An increase in the compression speed from 7rpm to 49rpm also resulted in a corresponding decrease in hardness and tensile strength of the simvastatin FDDTs from 93.84 to 61.14N and from 55.91N to 32.03N for 10mg and 20mg simvastatin tablets, respectively (Figure 5.8). This was accompanied by an increase in friability of the tablets. At high tableting speed of 49rpm, tablets were found to fail the friability test. In addition, at the high compressional speeds of 49rpm, tablets were found to stick on the lower punch and showed a tendency to break during ejection. As a

consequence, the number of tablets compressed was not sufficient to allow complete tablet characterisation at the highest speed of 49rpm.

The porosity of the tablets increased with increase in tableting speed, contributing to the decrease in mechanical strength of the tablets. A decrease in tablet dwell time with increase in speed may have resulted in the observed decrease in tablet hardness and accompanying increase in porosity.

Table 5.11: Influence of increase in tablet turret speed on the characteristics of mannitol based simvastatin FDDTs

SIM dose	Turret (rpm)	Weight[1] (mg)	H[2] (N)	TS[3] N/mm^2	Friab[4]	DT[5] (sec)	Porosity (%)
10mg	7	205.57± 1.70	93.84± 8.08	0.2829	0.34	34.5± 5.9	17.80
	28	211.19± 4.69	100.38 ± 5.74	0.0915	0.47	30.7± 3.5	18.15
	49	192.68± 19.35	61.14± 26.28	0.0677	failed*	22.5± 5.2	23.29
20mg	7	303.93± 2.66	55.91± 4.48	0.1092	0.19	13.3± 3.7	21.85
	28	296.10± 3.65	41.48± 3.87	0.0811	0.30	17.8± 2.2	23.47
	49	283.47± 15.63	32.03± 9.05	0.0628	failed*	**	26.02

[1]weight variation, [2]Hardness, [3]Tensile strength, [4]Friability (% weight loss), [5]disintegration time, *7 tablets broke, **no sufficient tablets available to conduct all the characterisation tests

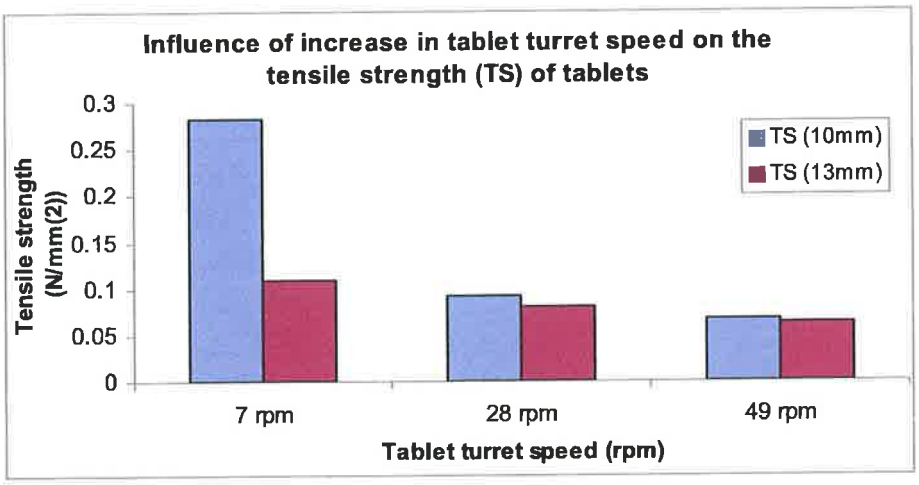

Figure 5.8: Influence of increase in tablet turret speed on the tensile strength of 10mm & 13mm simvastatin FDDTs

Simvastatin FDDTs using a combination of mannitol, M200 and Prosolv® in the ratio 1:1 as the filler and K-CLSF as the superdisintegrant was also studied at increasing tableting speed.The FDDTs contained simvastatin at a dose of 20mg per 300mg tablet weight. The tablets were compressed at a CF of 10kN using 13mm FBE toolings. The rationale for this combined filler was based on our earlier observations that both M200 FDDTs and Prosolv® based FDDTs have strong mechanical properties and low DTs. However, Prosolv® based FDDTs are reported to have poor palatability due to their cellulose compostion (Bi et al., 1999), while M200 being a sugar has a sweet taste with a pleasant and cooling mouthfeel, associated with its negative heat of solution (Lieberman et al., 1990).

The characteristics of the FDDTs formulated given in Table 5.12 show similar results to the M200 FDDTs formulated at higher tableting speed, Table 5.11 above. An increase in tablet turret speed from 7rpm to 49rpm resulted in an increase in weight variability from 0 to 5.5%, which was similar to the variability observed for corresponding M200 tablets, Table 5.11. Similar to the data observed for M200 FDDTs, a decrease in hardness of the tablets from 83.35 to 51.33N was observed with increase in tableting speed. DT of the tablets was found to decrease while the

porosity increased, probably related to the decreased dwell time at higher compression speed.

Table 5.12: Influence of increase in tablet turret speed on the characteristics of simvastatin based on M200 and prosolv at 1:1

CS[1] (rpm)	Weight[1] (mg)	H[2] (N)	TS[3] (N/mm^2)	Friab[4]	DT[5] (sec)	Porosity (%)
7	303.10 ± 0.00	83.35 ± 10.39	0.1645	0.00	17.80 ± 1.2	21.09
49	287.40 ± 16.02	51.33 ± 6.59	0.1014	0.00	12.50 ± 1.2	26.56

[1]weight variation, [2]hardness, [3]tensile strength, [4]friability (% weight loss), [5]disintegration time

A decrease in tensile strength when the tablet compression speeds was increased from 19 to 40rpm was reported by Akande et al., (1997). Similarly Tye et al., (2004) reported a decrease in tablet tensile strength, with an increase in porosity as the tableting speed increased from 3 to 19rpm.

Previous studies in our lab showed that placebo based tablets containing mannitol, K-CLSF and magnesium stearate were successfully tableted at high tablet turret speeds of 49rpm with little or no change in characteristics compared to corresponding tablets produced at 7rpm. In this study, at high tableting speed of 49rpm, the simvastatin FDDTs showed a weight variability of more than 5%. This was attributed to variability in flow of the tablet blend leading to variable die filling during tableting at high turret speeds. The addition of the hydrophobic simvastatin which has a small median particle size of 7.39μm and has elongated crystal morphology probably contributed to blend segregation and decreased flow when subject to higher vibrations at the higher tableting speed. The surface hydrophobicity of poorly soluble drugs can also lead to increased

cohesiveness affecting flowability and in addition can contribute to its poor dispersibility on contact with aqueous physiological medium. The Carr's index of simvastatin API was found to be 17.46%, which according to the scale of flowability (BP, 2008a) corresponds to a 'fair' flow, while the angle of repose for the simvastatin API was 52.70° indicative of poor flow.

One of the pre-requisites for successful formulation of FDDTs is fast dispersion, in particular of the active, into smaller primary particles, which could, in addition, lead to fast dissolution and enhanced bioavailability of the active. Spray drying has been successfully used to prepare biocompatible silica nanoparticles with enhanced flow properties and re-dispersibility (Kho and Hadinoto, 2009). Spray drying is also used for the preparation of DC excipients and powders with better compression properties by many DC base manufacturers (Gonnissen et al., 2007).

The formulation of simvastatin as a solid dispersion in a fast disintegrating matrix using spray drying was studied as a novel method to enhance the rheology and compressibility and to enhance the dispersibility of the hydrophobic drug from the resultant tablets or FDDTs.

The term 'solid dispersion' is applied to those systems in which drug particles are homogeneously distributed throughout a solid matrix (Kapsi and Ayres, 2001). Traditionally solid dispersions are prepared using a solvent in which both the drug and polymer or carrier is soluble. On drying, the drug usually tend to precipitate as amorphous drug in the polymer matrix giving rise to enhanced dissolution properties of the drug (Ambike et al., 2005). In this study, we formulated the solid crystalline simvastatin as a spray dried dispersion, using a suitable disintegrant carrier. The spray drying process was investigated as a way of producing such a matrix (Figure 5.9) which would, in addition, have improved rheological properties to allow further processing into a suitable dosage form, such as the FDDTs with resulting better disintegrant properties.

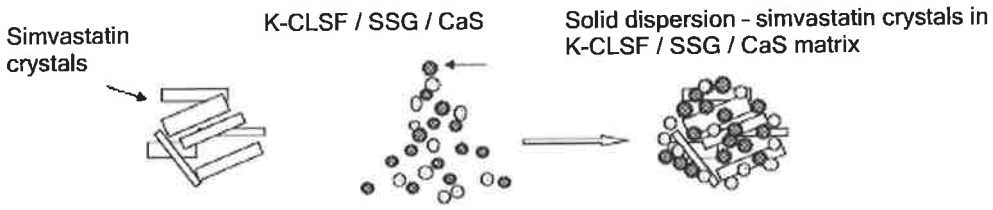

Figure 5.9: Schematic representation of the structure of rapidly disintegrating particles

5.5. Formulation and characterisation of simvastatin solid dispersions

Solid dispersions of simvastatin using the disintegrants Kollidon CLSF (K-CLSF), sodium starch glycollate (SSG), and calcium silicate (CaS) were prepared by a spray drying technique. Aqueous feed dispersions of drug and carrier were prepared as per the method outlined in chapter 2. Aqueous system was used in the preparation of solid dispersions (SDP) of simvastatin to prevent dissolution of the drug in the feed solution to avoid any conversion into its amorphous form. Earlier studies by Ambike et al., (2005) showed that spray drying of simvastatin in organic solutions led to the formation of amorphous product. Molecules in an amorphous form have high energy and are liable to be less stable than its crystalline low energy counterpart and consequently will tend to reconvert to the low energy, crystalline form. In addition aqueous solvent is regarded as environmentally and user friendly, and is economical.

Simvastatin (SIM) was spray dried with the superdisintegrant carriers at the drug to carrier ratios of 1:1 and total solids of 7.5%w/w. The inlet temperature of 90°C was used so as to maintain a low outlet temperature, as the Tg of simvastatin is reported to be at 35°C (Ambike et al., 2005; Patterson et al., 2008). The T_{outlet} during the spray drying was monitored and was in the range of 36 - 44°C (Table 5.13).

Table 5.13: Formulation and SD process parameters used for the preparation of solid dispersions of simvastatin

Batch	Disintegrant carrier used	FFR (%)	AAR (%)	T_{outlet} (°C)
SIM36	Kollidon CL-SF	16	100	37
SIM46	Sodium starch glycollate	16	100	44
SIM41	Calcium silicate	16	100	36
SIM API	Not applicable	16	100	29

Prior to spray drying, the particle size of the carriers used in dry form and in suspension with/without simvastatin was characterised. The solubility of simvastatin in the aqueous dispersions was also analysed.

The particle size of simvastatin and various carriers as received is illustrated in Table 5.14. Median particle size of simvastatin API was 7.39µm, with a span value less than 1.8. K-CLSF had a marginally greater median particle size of 11.73µm. The largest median particle size was observed for SSG at 42.66 µm, while CaS had the smallest median particle size at 4.06µm. Both K-CLSF and CaS had a particle size which was fairly close to the particle size of simvastatin.

Table 5.14: Particle size analysis of the raw materials used in the formulation of simvastatin SDP

Drug/carrier	D10% µm	D50% µm	D90% µm	SPAN
Simvastatin	2.65 ± 0.06	7.39 ± 0.03	15.28 ± 0.01	1.71 ± 0.01
K-CLSF	4.82 ± 0.09	11.73 ± 0.03	32.09 ± 0.40	2.32 ± 0.04
SSG	23.16 ± 0.33	42.66 ± 0.41	74.14 ± 0.81	1.20 ± 0.01
CaS	1.66 ± 0.09	4.06 ± 0.16	9.31 ± 0.24	1.89 ± 0.04

When formulated as aqueous dispersions, simvastatin API showed a larger median particle size of 16.08µm (Table 5.15) greater than its dry particle size at 7.39µm (Table 5.14). The D90% for the aqueous dispersion of simvastatin (SIM) API was found to be higher at 143µm.

The particle size distribution for the aqueous dispersions of SIM was found to be less uniform, indicative from its high span value of 8.67. This could be due to inefficient dispersibility of simvastatin API in the aqueous medium, due to the hydrophobic nature of the drug. No wetting agent or surfactant was added to the dispersion for the measurement.

Similarly, the median particle size of the simvastatin:carrier dispersions showed increased particle size for D10%, D50% and D90%. Dispersion containing sodium starch glycollate showed a considerably higher median particle size, D50% of 104.21μm. In comparison, feed solution consisting K-CLSF had a D50% of 25.15μm. This can be attributed to the high swelling capacity of SSG in aqueous medium, in comparison to K-CLSF (Zhao and Augsburger, 2006). Feed dispersion comprising simvastatin and CaS as a carrier showed the lowest median particle dimension of 12.75μm, lower than for simvastatin API aqueous dispersion. It is possible that calcium silicate results in better dispersibility of the simvastatin. A lower span value of the various feed dispersions compared to that of the aqueous dispersions of simvastatin API was noted, which is probably indicative of better dispersion of simvastatin API in the presence of the hydrophilic carriers.

Table 5.15: Particle size analysis of aqueous dispersions of simvastatin and disintegrants at drug to carrier ratio of 1:1

Feed dispersion	D10% (μm)	D50% (μm)	D90% (μm)	Span
Simvastatin	4.98±0.93	16.08 ±1.78	143.01±18.5	8.67±1.65
SIM + K-CLSF	6.03±0.04	25.15 ±0.39	67.10 ±1.95	2.43±0.05
SIM + SSG	16.54±0.35	104.2 ±3.94	233.26 ±2.63	2.79±0.42
SIM + CaS	3.11±0.14	12.75 ±0.41	35.37 ±0.42	2.53±0.04

Solubility of simvastatin API in DI water and in the presence of various carriers was examined in order to evaluate the influence of the presence of carriers on the aqueous solubility of simvastatin. Feed solutions/dispersions were prepared as per the procedure employed for the formulation of various SDP by spray drying and is outlined in methods section 2.1.3. chapter 2. One ml of the dispersions was withdrawn and filtered through the 0.45μm Hydrophilic PVDF filter before assaying by HPLC analysis (section 2.1.5.10, chapter 2).

The aqueous solubility of simvastatin API was found to be 28.75μg/ml (Table 5.16), which is close to the literature value of 30μg/ml (O'Neil, 2006). In the presence of the superdisintegrant carriers and dispersing agent, the solubility of simvastatin was found to be reduced by > 20 fold to below 0.49μg/ml except for CaS where a solubility of 3.39μg/ml was measured. This could be due to the presence of hydrophilic excipients possibly causing a salting out effect on the solubility of hydrophobic simvastatin.

Table 5.16: Solubility tests for aqueous dispersions consisting of simvastatin API in combination with disintegrant carriers

Feed solution /dispersion	Drug : carrier ratio	Solubility (μg/ml)
SIM	-	28.75 ± 4.25
SIM + K-CLSF	1:1	0.26 ± 0.44
SIM + SSG	1:1	0.49 ± 0.50
SIM + CaS	1:1	3.39 ± 1.59

5.6. Characterisation of simvastatin solid dispersions

An aqueous dispersion consisting of simvastatin API alone were first spray dried as per the procedure summarised in methods section 2.1.3., chapter 2. Spray drying of the aqueous dispersion of simvastatin API did not result in

degradation of simvastatin, as shown by the HPLC trace of spray dried simvastatin compared with the unprocessed simvastatin (Figure 5.10). The yield of spray dried simvastatin was high at 60.40% (Table 5.17), probably due to the lowest Toutlet of 29°C (Table 5.13).

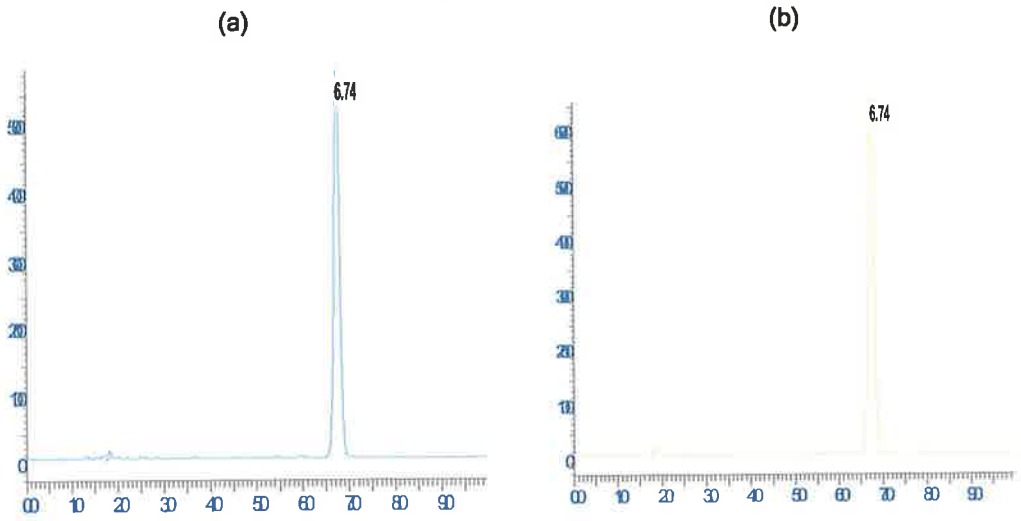

Figure 5.10 HPLC chromatogram for (a) simvastatin API - 0.25 mg per ml (b) Spray dried simvastatin (SIM56) - 0.20 mg/ml

The feed dispersions containing K-CLSF or SSG resulted in the low product yield at 21.07% and 21.87%, respectively, compared to the relatively higher product yield of 27.73% for the feed dispersions containing CaS as a carrier. In all cases, the product yield was lower than the product yield of 60.40%, obtained for the feed dispersions containing simvastatin API alone.

The drug content in the formulated SDP was found to be high at 90.75 and 95.80% for K-CLSF and CaS, respectively. While for SDP containing SSG, the drug content was higher at 143.18% (Table 5.17). This high drug content can be related to the loss of the swelled SSG in the spray drying chamber. This observation was found to be similar to an earlier study where loss of SSG was reported when spray drying aqueous suspensions containing SSG (Gonnissen et al., 2008). The authors state that swelled SSG could have led to the formation of comparatively coarser gel-like droplets during spray drying,

and hence causing partial drying of these droplets leading to its preferential deposition on the spray dryer chamber walls.

Table 5.17: Percentage recovery of spray dried SIM and its SDP and SIM content of SDPs

Drug/ carrier	Batch	Yield (%)	Theoretical content(%)	Assayed content (%)	Drug content (%)
SIM (SD)	SIM56	60.40	-	-	
K CL-SF	SIM36	21.07	50	45.36 ± 0.11	90.75 ± 0.24
SSG	SIM46	21.87	50	71.59 ± 4.79	143.18±9.58
CaS	SIM41	27.73	50	47.89 ± 3.11	95.80 ± 6.24

5.6.1. Particle size of solid dispersions

Particle size of the spray dried simvastatin and its corresponding SDP was measured and is outlined in Table 5.18. No significant difference was noticed between the median particle dimensions of simvastatin API of 7.39μm and spray dried SIM, which was 7.19μm. Particle size of the resultant SDP was found to be dependent on the type of carrier used.

Among the various carriers, incorporation of superdisintegrant carrier, K-CLSF generated product with significantly greater median particle size at 12.09μm compared with the simvastatin API at 7.39μm or other SDP ($p < 0.0001$).

The median particle size of SDP comprising SSG was 7.45μm and was found to be nearly similar to the raw drug at 7.39μm, despite reasonable significant difference ($p < 0.005$) between the mean particle dimensions of respective feed dispersions (Table 5.15). This low median size observed was unexpected as SSG has a high median particle size and was related to the loss of larger SSG particles during the spray drying process. The median

particle dimensions of the solid dispersions comprising CaS at 5.76μm, was found to be lower than the simvastatin API at 7.19μm and related to the smaller size of CaS. In addition, the dispersing mechanism of the CaS probably contributed to this low particle size.

The particle size distribution of SDP was found to be uniform as shown by the low span values observed at 1.68-2.09. It is a well documented fact that particle size and size distribution plays an important role in dictating flow properties of the product. Narrow size distribution can help in uniform mixing and therefore can contribute to homogenous drug distribution, hence resulting in tablets with uniform drug content when subjected to tableting (Whiteman and Yarwood, 1988).

Table 5.18: Particle size and size distribution of spray dried (SD) SIM and its SDP in various carriers at drug to carries weight ratio of 1:1

Drug /Carrier	Batch	Particle size analysis (μm)			SPAN
		D10%	D50%	D90%	
SIM (SD)	-	2.62 ± 0.05	7.19 ± 0.07	14.96 ± 0.71	1.72 ± 0.15
K-CL-SF	SIM36	4.97 ± 0.29	12.09 ± 0.55	25.30 ± 1.06	1.68 ± 0.03
SSG	SIM46	3.11 ± 0.06	7.45 ± 0.19	17.20 ± 1.15	1.89 ± 0.10
CaS	SIM41	1.81 ± 0.12	5.76 ± 0.42	13.85 ± 1.11	2.09 ± 0.08

5.6.2. Morphology of solid dispersions

Morphology of the SDP, as observed under the scanning electron microscope, showed the presence of elongated crystals (Figure 5.11a), and was found to be in agreement with the observations made by Jun et al., (2007).

The morphology of SDP produced using the superdisintegrant carrier, K-CLSF, was irregular. The presence of crystals apparent in the SDP containing

SSG were attributed to simvastatin which was at high content in this SDP. Simvastatin-CaS SDP showed spherical particulate morphology with indents.

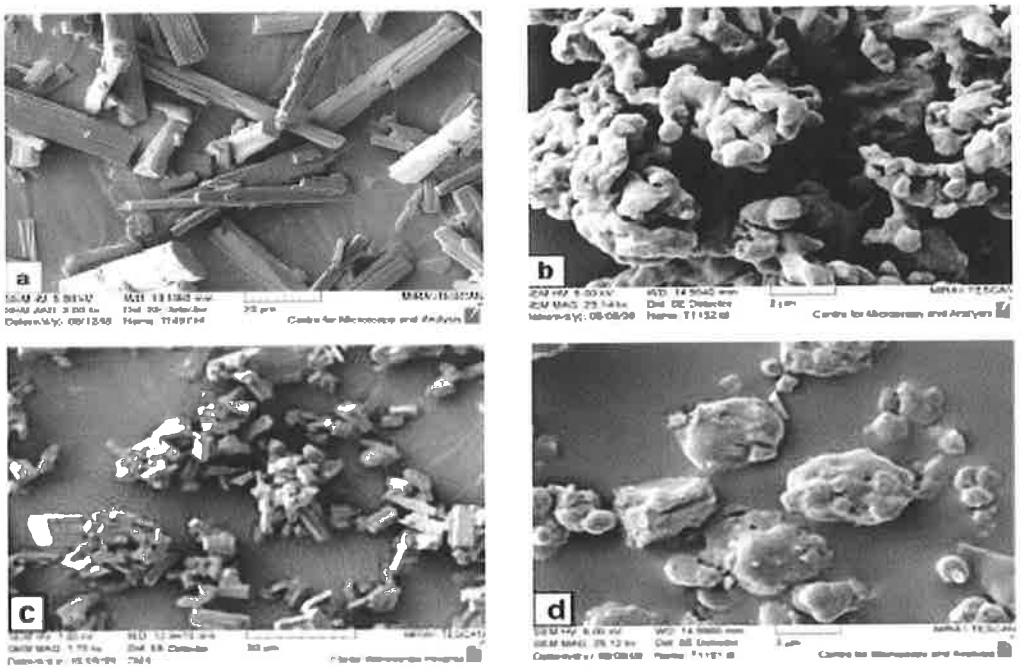

Figure 5.11: Electron micrographs of (a) unprocessed simvastatin and its SDP prepared at drug to carrier weight ratios of 1:1 using superdisintegrants (b) K-CLSF, (c) SSG, and (d) the dispersing agent CaS.

5.6.3. Density and rheological property of solid dispersions

Rheology of the product is a critical parameter for formulation of uniform weight tablets at high tableting speeds and a free-flowing powder can give lowest tablet weight variability (Doelker et al., 1995). In the present study, Carr's index value was used as an indicator of the rheological property of the formulated SDP. Carr's index was derived from the bulk and tapped density values of individual product.

From the data in Table 5.19, K-CLSF and CaS SDP showed improved rheological property compared to the native drug. The lowest bulk density of the SDP comprising K-CLSF suggests that particles could fit more compactly (Broadhead et al., 1992), while the SDP consisting CaS were found to be

denser which was probably linked to the small particle size of the product. The SDP based on either K-CLSF or CaS had the lowest Carr's index value and hence excellent rheology (Table 5.19).

In contrast, SDP containing SSG showed nearly similar Carr's index as the simvastatin API; this possibly related to the presence of the higher drug content in this SDP (Table 5.17).

Table 5.19: Density and rheological property of simvastatin and its SDP prepared in various carriers at drug to carrier ratio of 1:1 by spray drying

Carrier/drug	Batch	Bulk density (g/cc)	Tapped density (g/cc)	Carrs index (%)	Flow character[a]
Simvastatin	-	0.2169 ± 0.02	0.2629 ± 0.02	17.50	Fair
K-CL-SF	SIM36	0.1172 ± 0.00	0.1230 ± 0.00	4.72	Excellent
SSG	SIM46	0.1598 ± 0.01	0.1976 ± 0.01	19.13	Fair
CaS	SIM41	0.2500 ± 0.00	0.2778 ± 0.00	10.01	Excellent

[a] Carr's Index flowability: </= 10%, excellent; 11-15%, good; 16-20%, fair; 21-25%, poor, fluid; 26-31%, poor, cohesive; 32-73%, very poor; >38%, extremely poor.

5.6.4. Differential scanning calorimetry (DSC)

Spray drying can influence the crystalline nature of the drug, as has been reported by many authors (Corrigan et al 1984, Ambike et al., 2005; Patterson et al., 2008). DSC analysis was conducted to ascertain the polymorphic nature of the drug in the SDP.

DSC analysis was carried out on individual components, SDP, and on corresponding selected binary physical mixtures of drug/carrier to assess any possible interactions.

DSC analysis conducted on the simvastatin (SIM) API and spray dried (SD) simvastatin revealed a sharp endotherm corresponding to the melting point of the crystalline drug (Figure 5.12 & Table 5.20). The melting point of both simvastatin API and spray dried simvastatin was found to be 140.01°C, which

was found to be close to the literature value of 139.5°C (Jun et al., 2007). When SIM API and SIM SD were reheated (after cooling in DSC), a glass transition at 34.70°C corresponding to the Tg of the drug was observed. This was found to be similar to the literature value of 35°C reported by Ambike et al., (2005). The reheated thermogram of the simvastatin API and its spray dried version were similar indicating that spray drying of the aqueous dispersions of simvastatin alone did not affect the crystallinity of the drug.

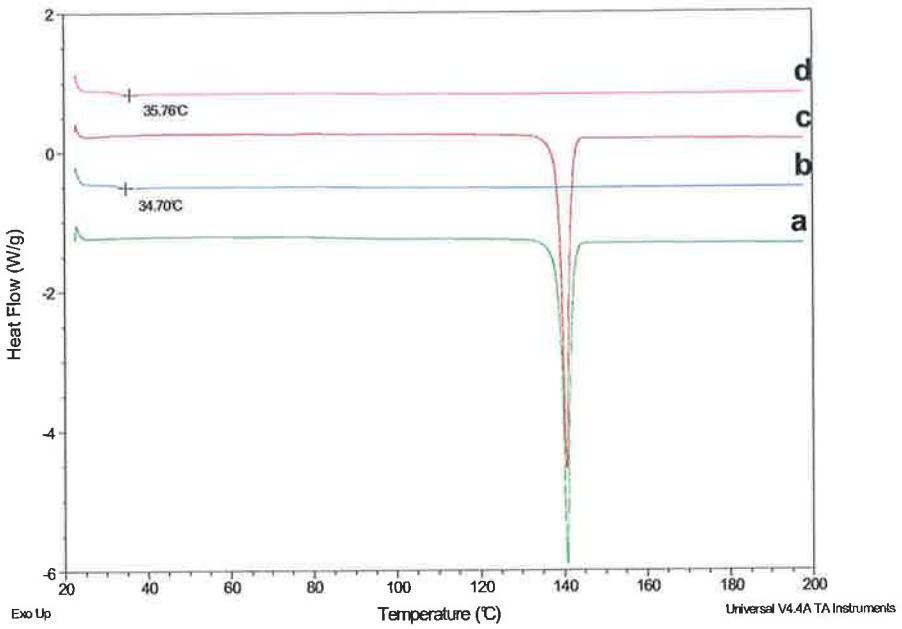

Figure 5.12: DSC thermogram of (a) simvastatin API, (b) SIM API on reheating, (c) spray dried SIM, (d) spray dried SIM on reheating

The DSC scan of the single component of the superdisintegrant carrier K-CLSF revealed a shallow broad endotherm (Figure 5.13). The DSC thermograms of the physical mixtures of simvastatin with K-CLSF at drug to carrier weight ratios of 1:1 showed the two different events, similar to those observed for the individual SIM and K-CLSF. Similar observations were made in its corresponding SDP, confirming that spray drying of aqueous dispersion of simvastatin with K-CLSF did not result in a change in crystallinity of simvastatin. The peak temperature of the event and its associated enthalpy of

fusion for pure carrier, and its respective physical mix and solid dispersions are outlined in Table 5.20.

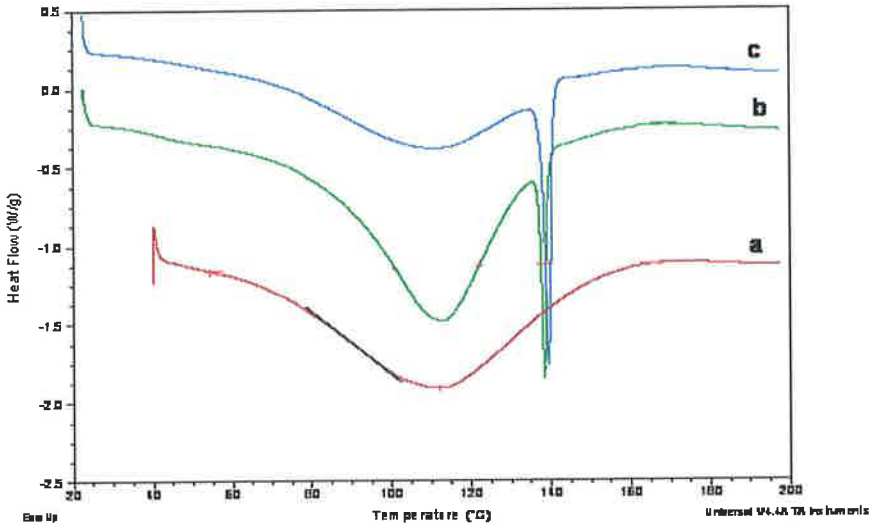

Figure 5.13: DSC thermogram of (a) Kollidon CLSF, (b) SDP of simvastatin with K-CLSF (SIM36), (b) its corresponding physical mix, at drug to carrier weight ratio of 1:1

Table 5.20: DSC data for K-CLSF, SDPs and corresponding physical mixtures

Drug/Carrier composites	Drug to carrier weight ratios	Peak temp. (°C)	Enthalpy of fusion ΔH_{fus} (J/g)
K-CLSF (alone)	-	111.97	235.4
Physical mixture	1:1	109.25	57.64
		139.47	20.75
Solid dispersions	1:1 (SIM36)	113.02	140.2
		138.41	12.03

The DSC thermogram of SSG presented in Figure 5.14, exhibited a shallow broad endotherm typical of amorphous substances (Moneghini et al., 2002). DSC thermogram of the physical mixture of simvastatin with SSG at drug to carrier weight ratios of 1:1 displayed two peaks corresponding to its

respective pure component (Figure 5.14 and Table 5.21), whereas its corresponding SDP just revealed one peak during the DSC studies, corresponding to the simvastatin API. The absence of an endothermic peak corresponding to the SSG can be due to the loss of SSG during spray drying, as described above in Table 5.17.

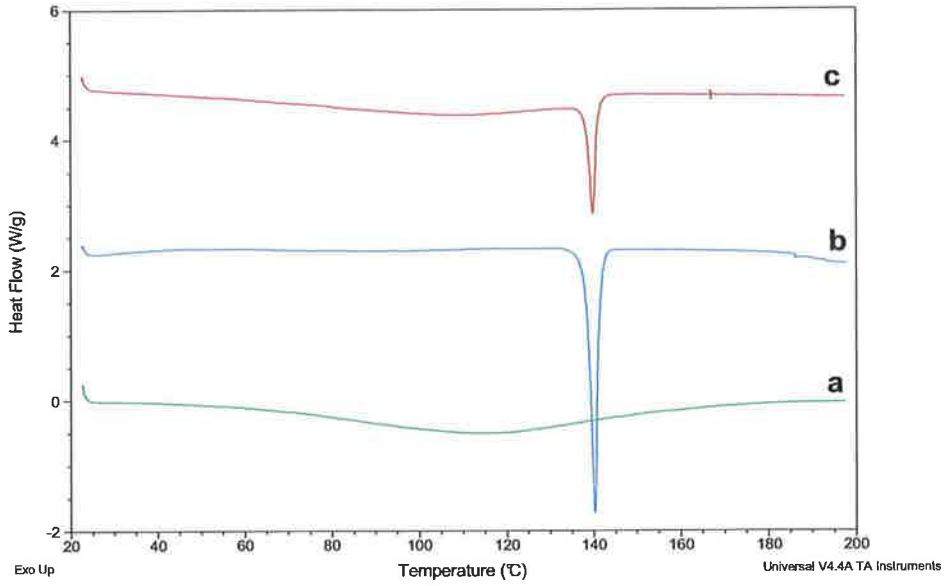

Figure 5.14: DSC thermogram of (a) SSG, (b) SDP of simvastatin with SSG (SIM46), and (c) its corresponding physical mix

The DSC thermogram for CaS did not reveal any event, as was reported by Sharma et al., (2005). This phenomenon is related to its relatively high melting point of 1700°C (Huber engineered materials). The DSC thermogram of the physical mixture of simvastatin with CaS at the drug to carrier weight ratio of 1:1 and of corresponding SDP showed only one endothermic event at 140.15°C, related to the SIM melting point (Figure 5.15 and Table 5.21).

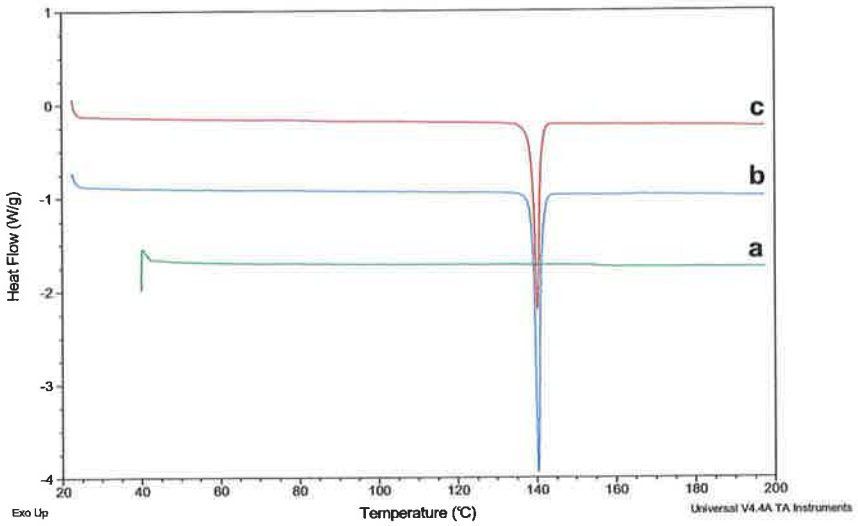

Figure 5.15: DSC thermogram of (a) calcium silicate, (b) SDP of simvastatin with calcium silicate (SIM41), and (c) its corresponding physical mix at drug to carrier weight ratio of 1:1

Table 5.21: DSC data for SSG, and dispersing agent, CaS, and its corresponding SDP and physical mix

Drug/ carrier	Drug/Carrier composites	Drug to carrier weight ratios	Peak temp. (°C)	Enthalpy of fusion ΔH_{fus} (J/g)
SSG	Alone	-	115.04	181
	Physical mixture	1:1	103.32	48.20
			139.88	21.53
	Solid dispersions	1:1 (SIM46)	140.16	56.06
Calcium	Physical mixture	1:1	140.15	22.25
Silicate	Solid dispersions	1:1 (SIM41)	140.29	31.08

5.6.5 X-ray powder diffraction (XRPD) of solid dispersions

X-ray powder diffraction was carried out on the simvastatin API and its corresponding SDP as per the procedure outlined in methods section 2.1.5.5, chapter 2.

The X-ray diffraction of the simvastatin API showed the presence of numerous distinct peaks at different diffraction angles of 2θ, corresponding to crystalline simvastatin (Figure 5.16). This was similar to the XRD reported in the literature (Jun et al., 2007; Patel and Patel, 2008).

XRPD patterns of the physical mixtures of simvastatin with K-CLSF, SSG, or CaS can be regarded as a simple superimposition of the individual components, with the presence of all the characteristic peaks corresponding to crystalline simvastatin API (Figure 5.16).

XRPD pattern of the solid dispersions of simvastatin in K-CLSF or SSG or CaS was found to be almost similar to its physical mixture, indicating the presence of simvastatin in its original form. Therefore, it can be said that the use of any of the three carriers (viz K-CLSF, SSG or CaS) did not alter the crystalline nature of the drug, supporting the presence of crystalline simvastatin in these SDP as demonstrated by DSC studies above in section 5.6.4.

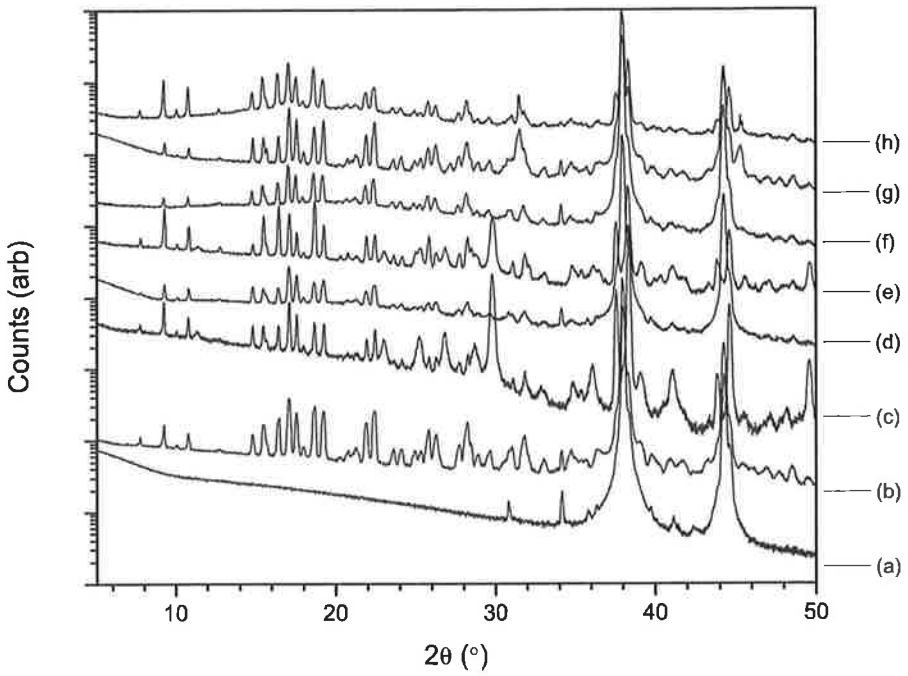

Figure 5.16: X-ray powder diffraction patterns of (a) background measurement, (b) simvastatin, physical mixture of simvastatin with (e) CaS, (f) K-CLSF, (h) SSG and corresponding SDP of simvastatin with (c) CaS, (d) K-CLSF, (g) SSG

5.6.6. Hot stage microscopy (HSM) studies of solid dispersions

Hot stage microscopy (HSM) was performed to assess the crystallinity/amorphous nature of SIM in the corresponding SDP. HSM studies were carried out as per the method outlined in methods section 2.1.5.6, chapter 2.

HSM pictures for the simvastatin API in Figure 5.17. show simvastatin crystals at room temperature (a), reflective of the crystalline nature of the drug. Subsequently, as the temperature increased, the crystals showed onset of melting at 130-133°C (b), and melting at 134-137°C (c). Complete melting was observed at 138-140°C (d). The melting point thus obtained was found to be similar to that observed during the DSC studies.

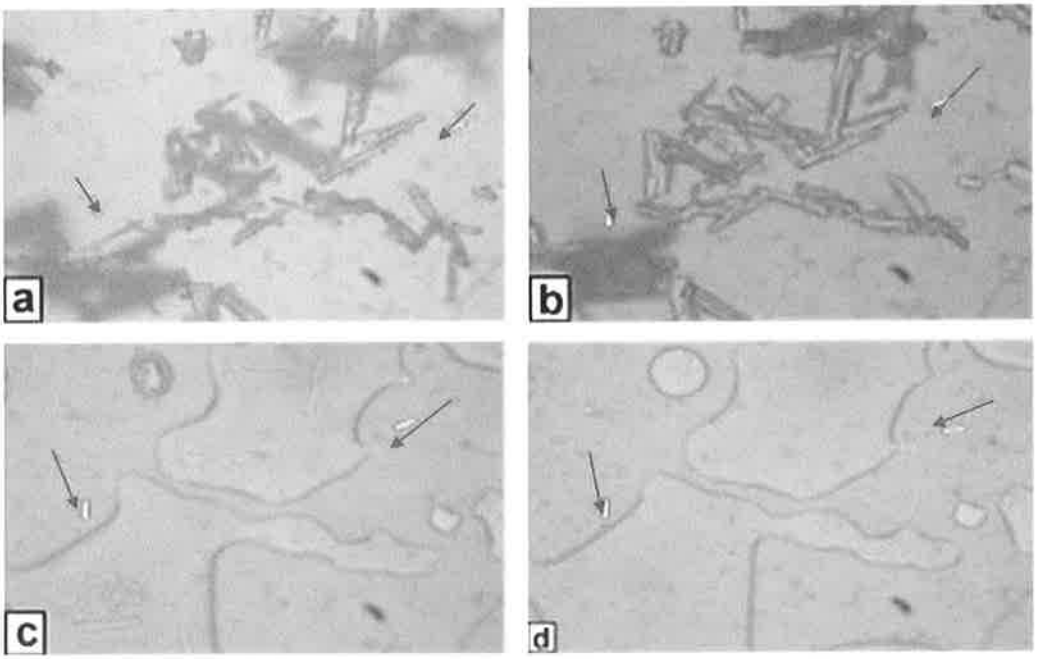

Figure 5.17: Hot stage microscopy pictures of unprocessed simvastatin (a) at room temperature, (b) at 130-133°C, (c) at 134 - 137°C, (d) at 138 - 140°C

Hot stage microscopy conducted on the SDP containing K-CLSF as a carrier Figure 5.18. show the presence of crystals at room temperature (a). The crystals were observed to melt as the temperature reached 130-133°C (b). At 138-140°C, the crystals fully melted. The temperature at which melting was observed was consistent with the melting point observed by DSC analysis.

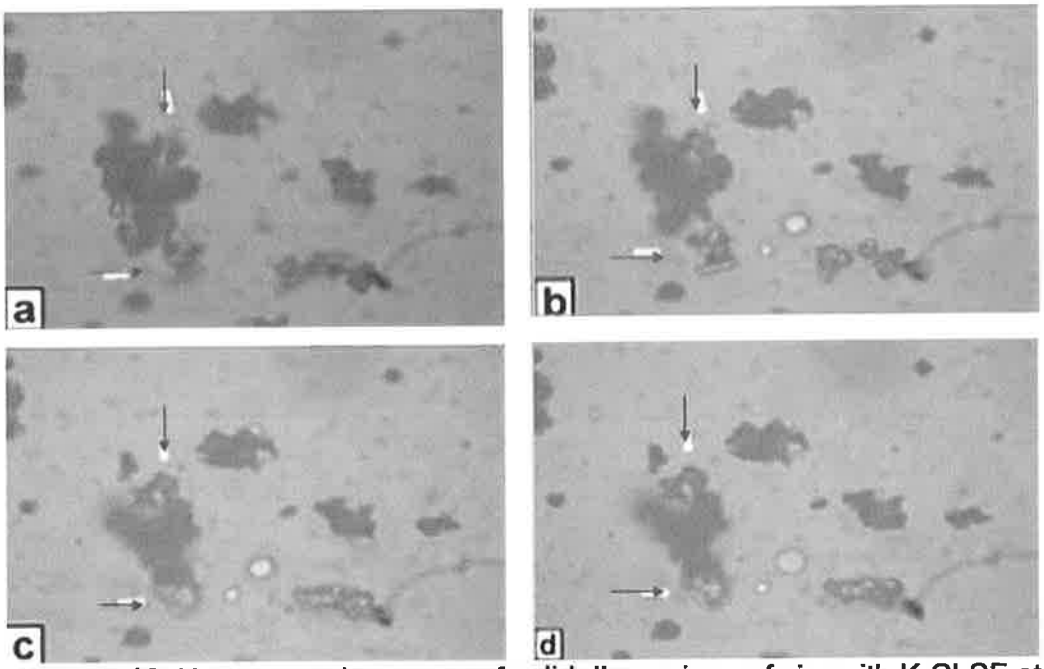

Figure 5.18: Hot stage microscopy of solid dispersions of sim with K-CLSF at drug to carrier ratio of 1:1, (a) at room temperature, (b) at 130 - 133°C (c) at 134 - 137°C, (d) at 138 - 140°C

HSM pictures of SDP of simvastatin and SSG showed the presence of crystals at room temperature (Figure 5.19a). As the temperature increased, onset of melting was observed at 130-133°C (Figure 5.19b) with melting completed at 138-140°C (d), confirming the presence of simvastatin in its crystalline form in the SIM-SSG SDP. The clear presence of crystals in this sample was attributed to the higher content of SIM, as shown by analysis of SIM content in Table 5.17.

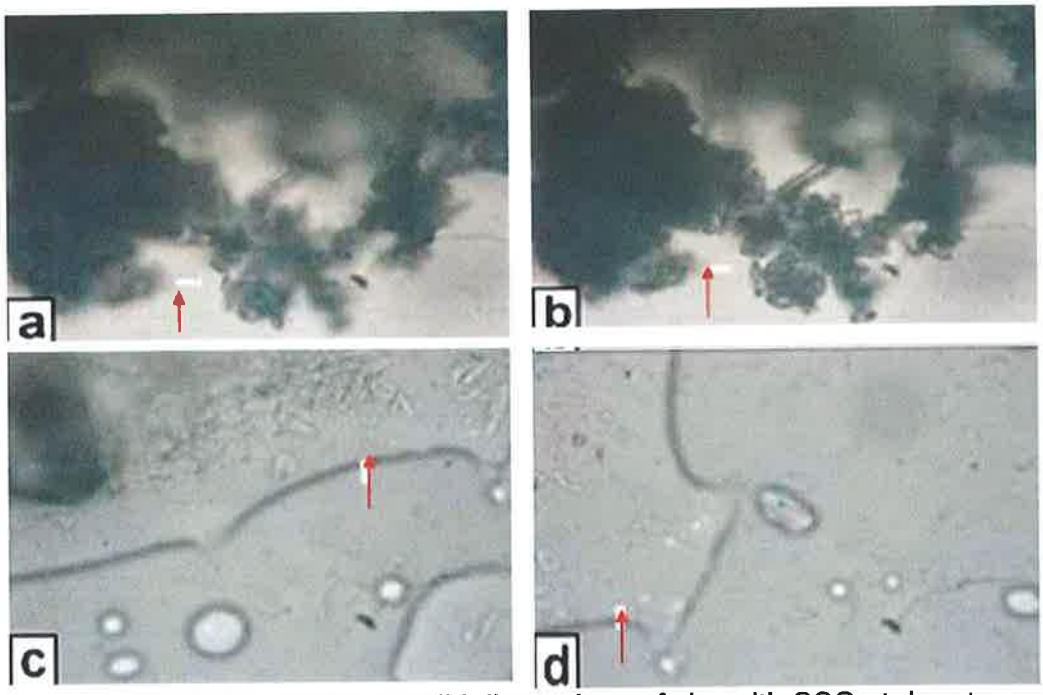

Figure 5.19: HSM pictures of solid dispersions of sim with SSG at drug to carrier ratio of 1:1 (a) at room temperature, (b) at 130 - 133°C (c) at 134 - 137°C, (d) at 138 - 140°C

HSM pictures of SDP of simvastatin in calcium silicate at drug to carrier ratio of 1:1 are outlined in Figure 5.20 was similar to the observations made for the other SDPs. SDP comprising calcium silicate demonstrated presence of crystals at room temperature. As the temperature rises, the crystals showed first signs of melting at 130-133°C with melting complete at 138-140°C. Simvastatin in these SDP was in crystalline form shown by DSC analysis and XRPD (Figure 5.15 and 5.16).

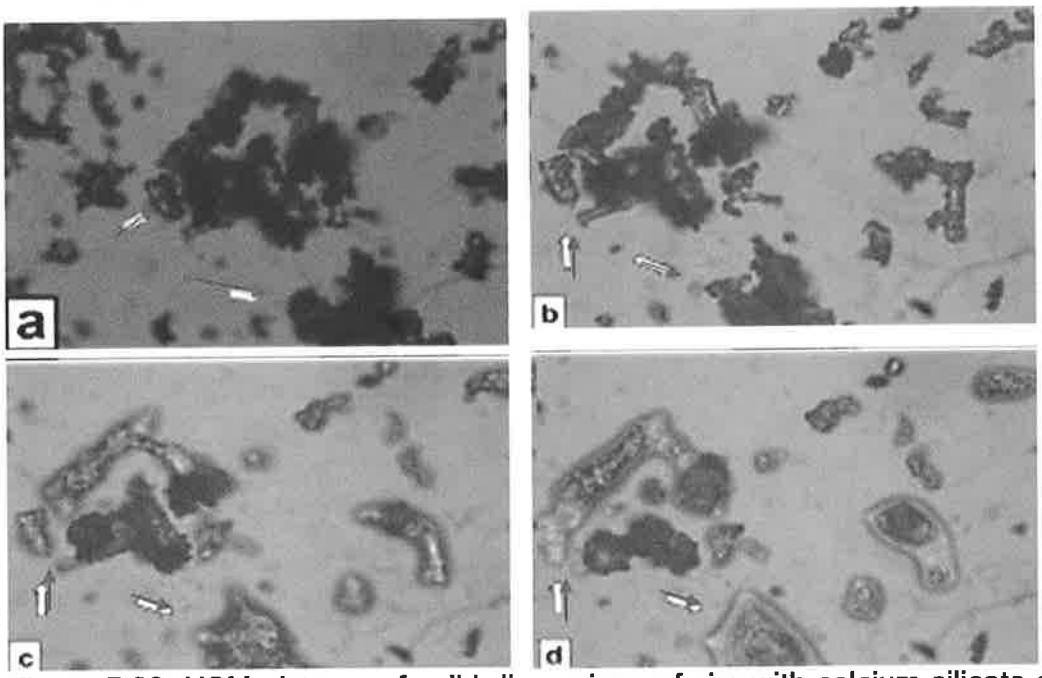

Figure 5.20: HSM pictures of solid dispersions of sim with calcium silicate at drug to carrier ratio of 1:1 (a) at room temperature, (b) at 130 - 133°C (c) at 134 - 137°C, (d) at 138 - 140°C

5.6.7. Fourier Transform Infra-Red (FT-IR) of solid dispersions

FT-IR studies were carried out to examine any potential interactions occurring between the drug and the carrier. FT-IR spectra of the individual components and physical mixture of the drug to carrier were compared with its corresponding SDP. FT-IR spectrum of the simvastatin API showed characteristic peaks corresponding to the various stretch and functional

groups (Figure 5.21, Table 5.22). These were consistent with the earlier reports by Adayeye CM, (1990); Ambike et al., (2005); Jun et al., (2007); Patel and Patel, (2008).

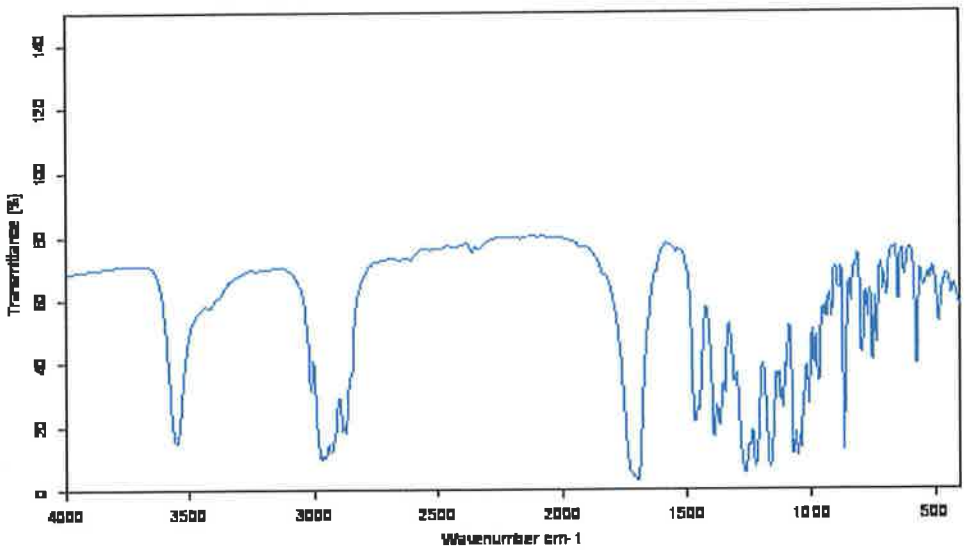

Figure 5.21: FT-IR spectra of unprocessed simvastatin

Table 5.22 Characteristic absorptions and corresponding stretch and functional group during FTIR studies of unprocessed simvastatin

Wavenumber (cm^{-1})	Attributions
3554	free O-H stretching vibrations
3445	associated O-H stretch
3011, 2967, 2870	olefinic C-H stretch, methyl C-H asymmetric stretch and methylene C-H symmetric stretch respectively
1717 and 1695	lactone C=O stretch and ester C=O stretch, respectively
1462 and 1391	methyl and methylene bending vibration
1263, 1215, 1163	lactone C-O-C stretch
1054	secondary alcohol C-O stretch

FT-IR spectra of K-CLSF and its respective SDP and physical mixtures at 1:1 are outlined in Figure 5.22. In case of K-CLSF, FT-IR spectrum showed a

narrow band at the wave number 3485cm^{-1} indicative of less hygroscopic nature of K-CLSF. In addition, it also showed characteristic band at the wave numbers 2959cm^{-1} and 1663cm^{-1}, related to C-H stretch and K-CLSF carbonyl, respectively (BASF). Further, the spectrum of the physical mixtures of simvastatin and K-CLSF was a superimposition of the respective components. FT-IR spectrum of corresponding SDP was found to be similar to that of the physical mixtures and hence did not indicate any interactions occurring between the drug and carrier.

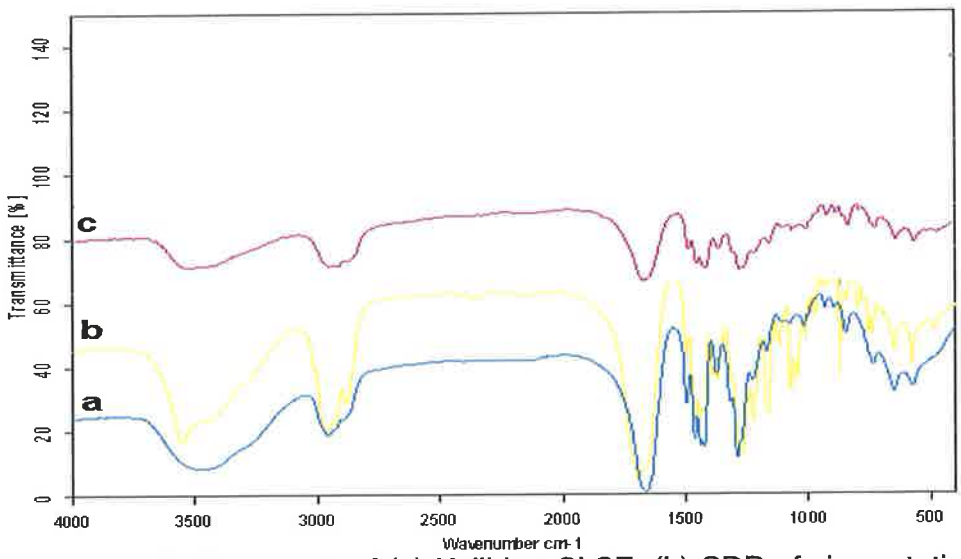

Figure 5.22: FT-IR spectra of (a) Kollidon CLSF, (b) SDP of simvastatin with K-CLSF (SIM36), (c) its corresponding physical mixtures at drug to carrier weight ratios of 1:1

Similar to SDP containing SIM and K-CLSF, the SDPs of SIM and SSG (Figure 5.23) and SIM and CaS (Figure 5.24) were similar to the spectra of the corresponding physical mixture of the respective components and did not indicate any interaction between simvastatin and the carrier.

The spectra observed for the individual carriers, SSG and CaS were similar to the spectra reported in the literature (Puttipipatkhachorn et al., 2005, De Sousa Meneses et al., 2006, Yu et al., 2004).

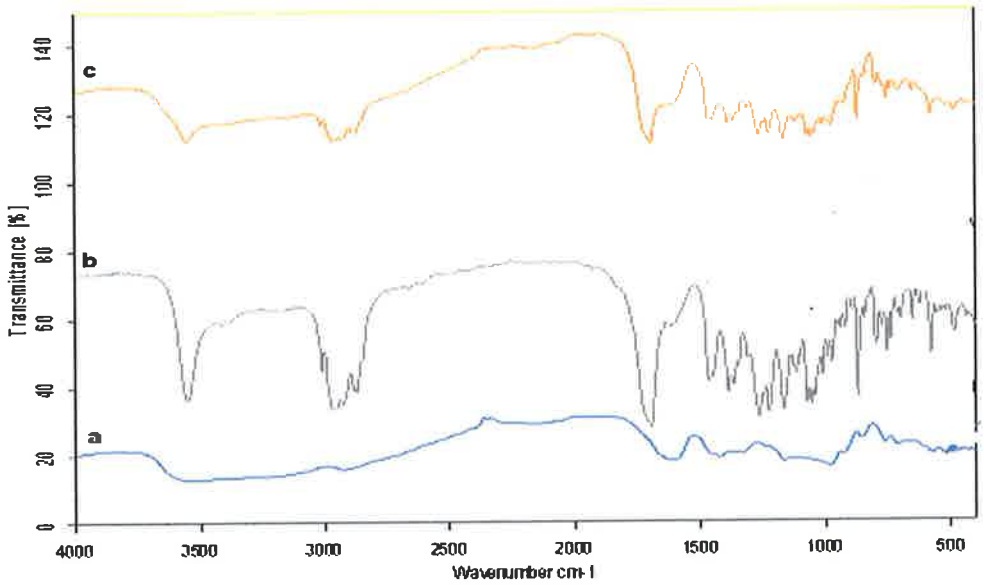

Figure 5.23: FT-IR spectra of (a) SSG, SDP of simvastatin with SSG at drug to carrier weight ratios of (b) 1:1 (SIM46), and its corresponding physical mixture at (c) 1:1

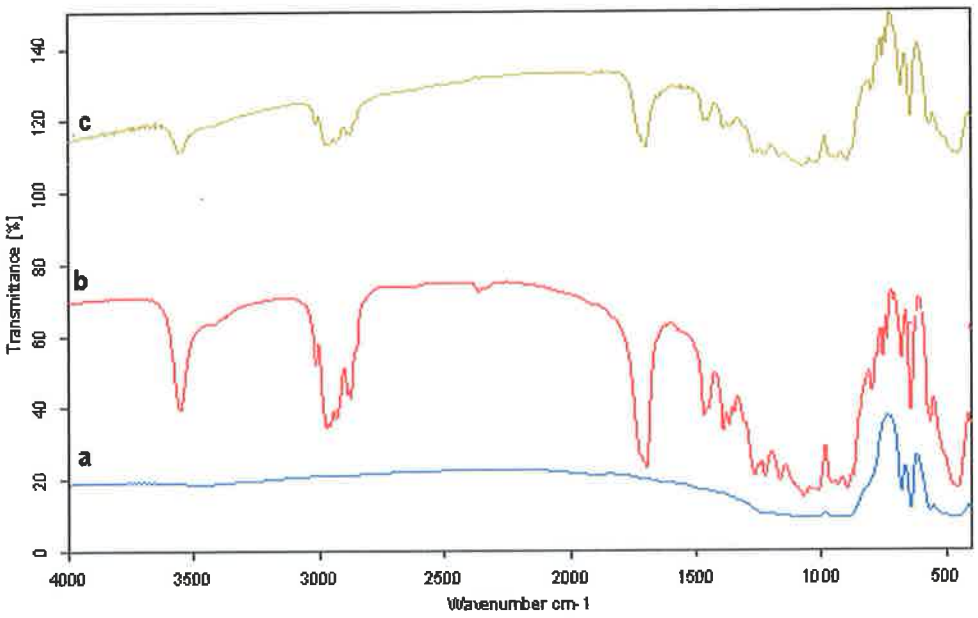

Figure 5.24: FT-IR spectra of (a) Calcium silicate, SDP of simvastatin with CaS at drug to carrier weight ratios of (b) 1:1 (SIM41), and its corresponding physical mixture at (d) 1:1

The FT-IR, DSC, XRD, HSM analysis of the SIM solid dispersions support the presence of unchanged crystalline simvastatin following spray drying of the aqueous dispersions containing SIM. The data did not indicate any possible interaction or degradation of the SIM following formulation as SDPs.

5.7. Conclusions

The influence of increasing simvastatin drug content on the characteristics of selected M200 and Prosolv® FDDT formulations were investigated. At the low tableting speed of 7rpm, tablets of uniform weight, low weight variation was obtained, irrespective of the formulation composition used. For the mannitol based formulations at 10mm, increasing simvastatin load did not affect the hardness and tensile strength of the tablets. Tablets containing K-CLSF were found to be harder at > 46N, compared to FDDTs containing Luquasorb® as disintegrant at < 30N. Increasing dose of simvastatin per tablet from 0 to 20mg caused an increase in the DT from 12 to 22 seconds, and 9.6 to 35.7 seconds, for K-CLSF and Luquasorb®, respectively. This was related to the decrease in the tablet porosity and presence of the hydrophobic drug, simvastatin. Yang et al (2004), had reported that inclusion of hydrophobic drug could increase the wetting time and hence can increase in DT of the tablets.

The FBE tablets containing K-CLSF or Luquasorb®, 10mm tablets containing simvastatin in the range 0 - 20mg (5 - 10%w/w) were found to be mechanically strong with low friability and DT ranging 12 - 35 seconds, while 13mm FBE simvastatin tablets containing 30mg dose (10%w/w) were found to be friable, with a lower DT of below 26 seconds. The lower mechanical strength was related to the lower thickness to diameter ratio.

For 13mm FBE Prosolv® based FDTs, the addition of simvastatin at 20mg (6.67%w/w) caused a decrease in hardness. A marginal increase in DT was also observed for each of the disintegrants, K-CLSF, SSG or SSG+CaS. Overall, the DT was found to be less than 11 seconds. All the FDDTs passed the test of friability.

Similar to the observations made for the placebo tablets (chapter 3), the simvastatin based Prosolv® tablets possessed higher hardness and lower disintegration time compared to the mannitol based tablets.

Remeron SolTab® which contains Mirtazepine an antidepressant, is prepared using OraSolv® technology. The tablet diameter is 9.7mm, and the DT reported was 56.6 seconds.

At the low tablet turret speed of 7rpm, the drug content of both, 10mm and 13mm FDTs, containing either mannitol or Prosolv® as a DC filler, was in the range of 90 - 108%, and were within BP 2008 specifications.

Prosolv contains 98%w/w of microcrystalline cellulose (MCC), which is insoluble in water and its mean particle size is 127µm. Bi et al (1999) reported that the use of MCC to prepare fast disintegrating tablets (FDTs) causes gritty feeling in the mouth.

Due to the aqueous solubility and good mouthfeel of mannitol, it was chosen as DC filler to investigate the influence of increase in tablet turret speed on the simvastatin FDDT characteristics. An increase in tablet turret speed resulted in variability in the characteristics of tablets. As the tablet turret speed increases from 7rpm to 49rpm, the tablet weight variation increased to > 10% and > 5% for 10mm/10mg and 13mm/20mg simvastatin FDDTs, respectively.

Placebo formulations in chapter 3 containing mannitol, K-CLSF and magnesium stearate were successfully tableted at high tablet turret speed of 49rpm and the tablets produced were reproducible in characteristics.

The SIM FDDT tablet hardness decreased from 93.84 to 61.14N and 55.91 to 32.03N, respectively, with a corresponding decrease in DT from 34.5 to 22.5 seconds for 10mm/10mg SIM FDDTs. The 13mm/20mg SIM FDDTs were friable and therefore, there were no enough tablets to allow measurement of the DT.

When SIM FDDTs were formulated using a combination of mannitol and Prosolv®, 1:1, as DC filler, 13mm FBE toolings, an increase in tablet turret speed from 7 to 49rpm caused a tablet weight variation of > 5%. A decrease in hardness from 83.35 to 51.33N was observed. The DT was found to increase from 12.5 to 17.83 seconds. In addition, at high compressional speeds of 49rpm the tablets appeared to stick on the lower punch, resulting in chipping of tablets during compression, probably attributed to relatively low hardness of the tablets formed at the higher tablet turret speed.

The increased variability in weight was related to the poor flow of simvastatin API probably due to its small particle size, 7.39μm, elongated morphology and hydrophobic surface, probably due to its poor solubility, contributing to increased cohesiveness. Therefore, an attempt was made to prepare crystalline solid dispersion of simvastatin in a hydrophilic fast disintegrating matrix by spray drying.

Solid dispersions (SDP) of simvastatin with hydrophilic superdisintegrant carriers had greater particle size of 12μm, and narrow particle size distribution contributing to improved rheology compared to simvastatin API. The lower

bulk density of the SDP reflects better compactibility. The drug content in these SDP was found to be high at > 90% for K-CLSF and CaS SIM SDPs. The drug content of SIM:SSG SDP was greater than 100% at 143%, which was related to the loss of the larger SSG particles during spray drying.

DSC and XRD showed no change in the crystallinity of SIM during spray drying aqueous dispersions of SIM and disintegrant carrier at the ratio 1:1. FT-IR studies did not show any potential interactions taking place between drug and the disintegrant carriers. Additional studies such as HSM reaffirmed the aforementioned results.

In the next chapter, the SDP of simvastatin with K-CLSF was used to formulate SIM FDDTs. These FDDTs were compared with the characteristics of the tablets prepared using physical mix of simvastatin and K-CLSF. The influence of the increasing tablet turret speeds on the characteristics of the tablets was investigated. Enhancement of the dispersibility of the simvastatin from the tablets containing the SDP was evaluated by dissolution studies and was compared with simvastatin release from the marketed simvastatin tablets, Zocor®.

CHAPTER 6

Validation of simvastatin FDDT formulations: Scale up and stability studies

6.0 Introduction

Scale-up and technology transfer of any successful formulation from a laboratory to production scale usually forms one of the most important, integral and challenging task of research and development process. The product is manufactured for further commercialization, hence, batch to batch reproducibility becomes very critical. It is also expected that the production of the formulation is done at high speed and at large scale, without any compromise in its product characteristics. The production of tablets is carried out in the industry using a rotary tablet press at a high speed of > 20rpm. It is a well known fact that the level of tablet turret speed can have a profound influence on the compression properties and hence characteristics of tablets (Heinz et al., 2000; Tye et al., 2004).

The studies in this chapter are designed to examine the influence of tablet production rate i.e. increase in tablet turret speeds on the properties of simvastatin FDDTs. Batch sizes was increased from 25g and increased to a scale to 150g, using promising formulations from Chapter 5. FDDTs formulated at high speed were examined for their stability profile over a 3-6 month period.

6.1. Results & Discussion

6.1.1 Formulation of tablets

It was concluded in Chapter 5 that an increase in tablet turret speed for the formulation containing simvastatin API in combination with Mannitol 200 and K-CLSF and magnesium stearate produced FDTs with variable characteristics. An increase in tablet turret speed from 7rpm to 49rpm resulted in an increase in variability of the tablet characteristics. A decrease in the tablet weight was related to the non-uniform flow of the tablet blend at high tablet turret speeds, probably related to the decrease in the dwell time. A corresponding decrease in hardness and DT was also observed. The non-

uniform flow of the tablet blend can be attributed to the small particle size, elongated morphology and hydrophobic surface of simvastatin. Placebo tablets of the same formulation were shown to scale up without any change in tablet characteristics.

The solid dispersions (SDP) of simvastatin were subsequently prepared in an attempt to enhance the flowability and compressibility of simvastatin API. In addition, the hydrophilic disintegrant carrier would help to disperse the tablet and drug on exposure to the aqueous medium. Among the various SDP produced in Chapter 5, SDPs of K-CLSF and CaS showed optimal drug content with high flowability. The SIM - K-CLSF SDP was selected for further formulation as SIM FDDTs and were compared with SIM API FDDTs prepared from the blend containing K-CLSF as a physical mix.

Incorporating a glidant, Aerosil®, is a conventional industrial technique of improving the rheology of tablet blend and this was evaluated for its potential to produce FDDTs of uniform and consistent weight at high compression speed.

The influence of increase in tablet turret speed from 7rpm to 49rpm on the characteristics of the tablets was investigated using a feeder speed of 30rpm. The fillers evaluated for the preparation of favourable FDTs were Mannitol 200 and a combination of Mannitol 200 with Prosolv® in the ratios 3:1 and 1:1.

The tablets were characterised for various tests, weight uniformity, hardness, DT, friability, thickness as outlined in chapter 2.

In this validation study, we characterised the disintegration time of tablets using both the modified BP 2008 method used for the conventional tablets (i.e. each tablet at a time), as used in the previous studies described in chapters 3-5. In addition, the test described for oral lyophilisates was also used to characterise the DT of the FDDTs. The dissolution of simvastatin from the FDDTs was examined as per the method described in the USP 2007/BP 2008.

6.1.2. Influence of increase in tablet turret speed on the characteristics of FDDTs

The formulation containing M200 or M200:Prosolv in the ratio 3:1 or 1:1 was compressed at the turret speeds of 7 and 49rpm, at 10kN using 13mm FBE tools to contain 20mg of simvastatin/300mg tablet. The characteristics of the tablets prepared using the SDPs of simvastatin and K-CLSF were compared with the tablets containing the corresponding physical mix prepared without and with using a glidant, Aerosil® (SiO_2).

For the FDDTs prepared using SDP of simvastatin, an increase in tablet turret speed from 7rpm to 49rpm caused an increase in tablet weight variability from 0.4 to 2.9% compared to an increase from 0.88 to 5.51% for the tablets prepared using physical mix of simvastatin and K-CLSF. While for the tablets prepared using a glidant, Aerosil®, and K-CLSF as physical mix, the Mannitol 200 (M200) based tablets showed a negligible increase from 0.81 to 0.83%. Similarly, for the M200+Prosolv FDDTs at 1:1 and 3:1, minor increase weight variability was from 0.99 to 1.88% and 0.28 to 0.66%, respectively (Table 6.1).

An increase in tablet turret speed from 7rpm to 49rpm caused a decrease in tablet hardness from 51.86 to 35.48N and 55.91 to 32.03N, for tablets containing SDP of SIM:K-CLSF and the corresponding physical mix, respectively. While, for tablets prepared using a glidant, Aerosil®, no significant change ($p > 0.05$) in the hardness was found for M200 based tablets, which was in the range 54.48 - 53.07N, whereas for M200:Prosolv based FDDTs at 3:1 and 1:1, a decrease in tablet hardness from 66.84 to 60.89N and 73.90 to 56.16N, respectively, was observed.

The increase in the Prosolv® content resulted in an increase in the tablet hardness as was expected.

Overall, during the friability studies a percent weight loss of less than 0.42% was observed.

At high tablet turret speeds of 49rpm, the tableting proceeded smoothly for either blend containing the solid dispersion or Aerosil®. The blend containing the physical mix of simvastatin and K-CLSF, without Aerosil®, showed sticking. The tablets produced were variable in characteristics and were of low hardness and tensile strength.

Table 6.1: Characteristics of FDDTs prepared at tabletting speed of 7rpm and 49rpm tabletting speed

Filler	RPM +	Weight (mg)	Hardness (N)	TS[1] N/mm^2	Friability	Porosity (%)
M200[2] (SDP-SIM)	7	304.80 ± 1.22	51.86 ± 3.89	0.1014	0.16	20.88
	49	296.23 ± 8.46	35.48 ± 9.83	0.0693	0.24	23.48
M200[3]	7	303.93 ± 2.66	55.91 ± 4.48	0.1092	0.19	21.85
	49	283.47 ± 15.6	32.03 ± 9.05	0.0628	*	26.02
M200[4] (SiO2)	7	303.70 ± 2.45	54.48 ± 4.24	0.1055	0.40	23.89
	49	304.70 ± 2.54	53.07 ± 5.62	0.1021	0.42	25.41
M:P[5] 3:1	7	307.66 ± 3.04	73.90 ± 3.84	0.1456	0.23	21.99
	49	295.20 ± 5.55	56.16 ±1.25	0.1114	0.03	23.21
M:P[6] 1:1	7	309.42 ± 0.86	66.84 ±1.74	0.1314	0.00	21.10
	49	303.67 ± 2.01	60.89 ±4.60	0.1198	0.13	22.18

[1]Tensile strength, [2]M200 FDDTs containing SDP of SIM and K-CLSF, [3]M200 based containing physical mix of simvastatin and K-CLSF (chapter 5), [4]M200 based containing physical mix of simvastatin and K-CLSF with Aerosil®, [5]containing mannitol and prosolv at 3:1 and Aerosil®, [6]containing mannitol and prosolv at 1:1 and Aerosil®, +tablet turret speed (rpm), *no sufficient tablets available to conduct all the characterization tests

The DT of the tablets was evaluated by using both the modified BP 2008 DT method for conventional tablets and the BP 2008 DT method for oral

lyophilisates. The modified BP 2008 DT test is generally used for the conventional tablets where the USP disintegration apparatus is used, while the DT measurement method for the oral lyophilisates utilises a beaker containing 200 mls of DI water at 15 - 25°C. This method could help us get an idea of as to how long will it take for the tablet to disintegrate if the patient does not masticate the tablet in his mouth. The DT of tablets under unagitated conditions was evaluated for selected batches formulated at 49rpm are given in Table 6.2.

The DT of M200 tablets containing SDP of SIM or Aerosil® was found to be in the range, 9 - 20 seconds, irrespective of the compression speeds. As the Prosolv® content increases from 0 to 25% and 50%, a marginal decrease in the DT was observed from 16.33 to 7.17 and 10 seconds, respectively (Table 6.2).

Overall, for FDDTs containing M200 and Prosolv® at 3:1 or 1:1, the porosity of the tablets was found to be in the range 21.10 - 23.21%, giving a DT of < 10 seconds. This was found to be consistent with the literature.
Grimshaw et al., (2008) used granulation matrix of microcrystalline cellulose and spray dried mannitol (Mannogem EZ) and compressed into 7mm flat-faced tablets. The authors reported the tablets with porosity 21.12 - 23.23% and DT of below 8 seconds.

The simvastatin content in our FDDTs was in the optimal range 92 - 104%.

Table 6.2: Disintegration times and simvastatin content of FDDTs prepared using SDP of simvastatin and blend containing simvastatin API and Aerosil®, compressed at 7rpm and 49rpm

Filler	RPM[+]	DT (seconds)	DT2[**] (seconds)	Assayed drug content (%)
M200[2]	7	19.17 ± 6.08	-	-
(SDP)	49	15.17 ± 3.49		92.91 ± 2.13
M200[3]	7	13.33 ± 3.67	-	-
	49			-
M200[4]	7	09.67 ± 3.56	-	102.02 ± 0.27
(SiO2)	49	16.33 ± 1.21	16.17 ±2.86	103.22 ± 0.22
M:P[5]	7	07.83 ± 0.98	-	-
3:1	49	07.17 ± 0.75	13.67 ±1.86	95.41 ± 0.26
M:P[6]	7	09.17 ± 0.75	-	-
1:1	49	10.00 ± 1.79	14.33 ± 2.58	99.24 ± 0.31

[**]DT2 = DT by beaker method, conducted as per the specifications in the EP2008 for oral lyophilisates

6.1.3. Stability studies of selected simvastatin FDDTs

The FDDTs which showed low weight variation, with maximum variability of 1.88% were selected for stability testing. The FDDT batches selected were formulations containing Aerosil® and prepared using M200, M200:prosolv at 3:1 and 1:1 ratios. The three selected batches showed high hardness >53 N and low DT <20 seconds. Tablets were stored in sealed securitainers under the uncontrolled laboratory conditions, bearing in mind that the laboratory temperature and humidity conditions usually changes with time. The characteristics of the tablets at intervals of time of t = 0, 1, 3 and 6 months were measured and are given in Tables 6.3 and 6.4 below.

There was an insignificant increase in weight of the tablets with time, this increase being greater for M200 tablets. A decrease in hardness of the FDDTs was observed over time, which was significant (ANOVA; $p < 0.05$) for the M200 based FDDTs from 53.07 to 40.55N.

The friability of the tablets was found to be below 1% in all cases and there was an increase in friability only for the Prosolv:M200 1:1 FDDTs from 0.13 to 0.65%, with time (Table 6.3).

Thickness of the tablets was found to be in the range 2.32 to 2.37mm for M200 based FDDTs, and in the range 2.13 to 2.18mm and 2.19 - 2.21mm, for mannitol:prosolv based tablets at 3:1 and 1:1, respectively.

Interestingly, the DT measured using both methods were similar for M200 FDDTs. In contrast, for FDDTs containing M200:Prosolv in the ratio 3:1 and 1:1, the DT measured using the static method of oral lyophilisates was higher than the DT value observed using the modified disintegration method for conventional tablets. This suggests that possibly, M200:Prosolv based FDDTs may require agitation or some mastication in vivo for fast disintegration. DT of the FDDTs was found to be in the range 16.33 - 19.17, 7.17 - 11.17 and 8.67 - 11 seconds for FDDTs based on M200, M200:Prosolv in the ratio 3:1 and 1:1, respectively (Table 6.4). While, the DT of the branded simvastatin, Zocor® tablets was 9 minutes 8 seconds as is expected for a conventional tablet.

The assayed simvastatin content showed no loss of simvastatin over time suggesting no degradation of simvastatin over the storage period examined (Table 6.4).

Table 6.3: Characteristics of 20mg SIM FDDTs with Aerosil® prepared at 49rpm on stability in securitainers at room temperature

Filler	Time (month)	Weight (mg)	Hardness (N)	TS[1] (N/mm^2)	Friability (%)	Porosity (%)
M200	0	304.70 ± 2.54	53.07 ± 5.62	0.1021	0.42	25.41
	1	308.10 ± 1.44	50.91 ± 4.83	0.0977	0.32	25.27
	3	308.01 ± 2.75	43.31 ± 2.68	0.0834	0.26	24.59
	6	310.21 ± 2.72	40.55 ± 3.16	0.0779	0.29	24.62
M:P	0	295.20 ± 5.55	56.16 ± 1.25	0.1114	0.03	23.21
3:1	1	296.06 ± 3.72	50.67 ± 3.82	0.1005	0.34	22.94
	3	297.25 ± 6.42	48.62 ± 7.75	0.0962	0.10	23.51
M:P	0	303.67 ± 2.01	60.89 ± 4.60	0.1198	0.13	22.18
1:1	1	305.34 ± 3.50	56.26 ± 6.15	0.1106	0.33	22.06
	3	306.14 ± 4.16	61.25 ± 5.03	0.1202	0.65	22.33

[1]Tensile strength

Table 6.4: DT and simvastatin content of 20mg SIM FDDTs containing Aerosil®, kept on stability in securitainers at RT

Filler	Time (month)	DT 1[1] (seconds)	DT 2[2] (seconds)	Assayed drug content (%)
Mannitol 200	0	16.33 ± 1.21	16.17 ± 2.86	103.22 ± 0.22
(M200)	1	14.33 ± 2.42	15.00 ± 2.76	-
	3	13.17 ± 0.98	14.83 ± 1.72	92.43 ± 0.55
	6	19.17 ± 5.98	11.00 ± 1.55	115.63 ± 7.67
Zocor 20mg		9min 8sec	-	110.52 ± 4.39
M200:prosolv	0	07.17 ± 0.75	13.67 ± 1.86	95.41 ± 0.26
3:1	1	07.33 ± 1.03	16.67 ± 1.37	-
	3	11.17 ± 1.33	12.67 ± 3.08	109.84 ± 0.61
M200:prosolv	0	10.00 ± 1.79	14.33 ± 2.58	99.24 ± 0.31
1:1	1	11.00 ± 1.10	16.83 ± 1.47	-
	3	08.67 ± 2.50	19.33 ± 2.58	114.20 ± 1.83

[1]DT1 = DT by modified BP 2008 method for conventional tablets; [2] DT2 = DT by beaker method, conducted as per the specifications in the EP2008 for oral lyophilisates

The increase in weight of the FDDTs with time was investigated using thermogravimetric analysis (TGA) to measure the percentage of residual moisture present in the product. A percentage weight loss of 0.52% was observed for the M200 FDDTs after 6 months storage (Table 6.5). The inherent moisture content of mannitol from its certificate of analysis showed a moisture content of 0.06%, which suggests a small uptake in moisture possibly over processing and storage although this uptake was not sufficient to account for the weight increase. This weight increase observed with time may be related to the normal weight variability of FDDTs during compression. For Prosolv:M200 FDDTs, the moisture content of the FDDTs after 3 months storage was 2.25 and 3.08% (Table 6.5). The inherent moisture content of Prosolv® from its certificate of analysis was 3.5%, which indicates a small uptake of moisture during processing and storage.

Table 6.5: Moisture content of FDDTs after storage measured using TGA

Filler	Time point (months)	Moisture content (%)
Mannitol 200	t = 6	0.5196 ± 0.0281
M200:prosolv 3:1	t = 3	2.2547 ± 0.2711
M200:prosolv 1:1	t = 3	3.0777 ± 0.1305

6.1.4. Dissolution of simvastatin from FDDTs formulated at high turret speed

The dissolution profiles of simvastatin FDDTs prepared at 49rpm were compared with the commercial innovator product, Zocor®. The cumulative amount of drug released against time is plotted in Figure 6.1.

As expected from the fast disintegration of the FDDTs compared with Zocor® tablets, the dissolution of simvastatin from the FDDTs formulated was faster, with > 78.13% of simvastatin released at 5 minutes compared with 19.27%

simvastatin released from the Zocor® 20mg tablets. The low amount of drug released for Zocor can be attributed to its exceptionally low disintegration time (20mg; 9minutes 8seconds) compared to the FDDTs of below 20 seconds

FDDTs formulated using SDP of simvastatin showed immediate release of all its simvastatin content after 5 minutes. In comparison 87.05% of simvastatin was released from the M200 FDDTs containing simvastatin API, while for FDDTs containing a combination of Mannitol 200 and prosolv in the ratios of 1:1 and 3:1, the amount of simvastatin released after 5 minutes was 90.82 and 78.13%, respectively. The data shown in this study supports the rationale for an FDDT formulation of simvastatin for a faster simvastatin release which may enhance its in vivo absorption and bioavailability. In addition, using a spray dried fast disintegrating matrix of simvastatin with K-CLSF resulted in an instantaneous release of simvastatin from the FDDTs showing that an intimate formulation of the hydrophobic drug with a hydrophilic disintegrant can result in a fast dispersibility and dissolution of the drug.

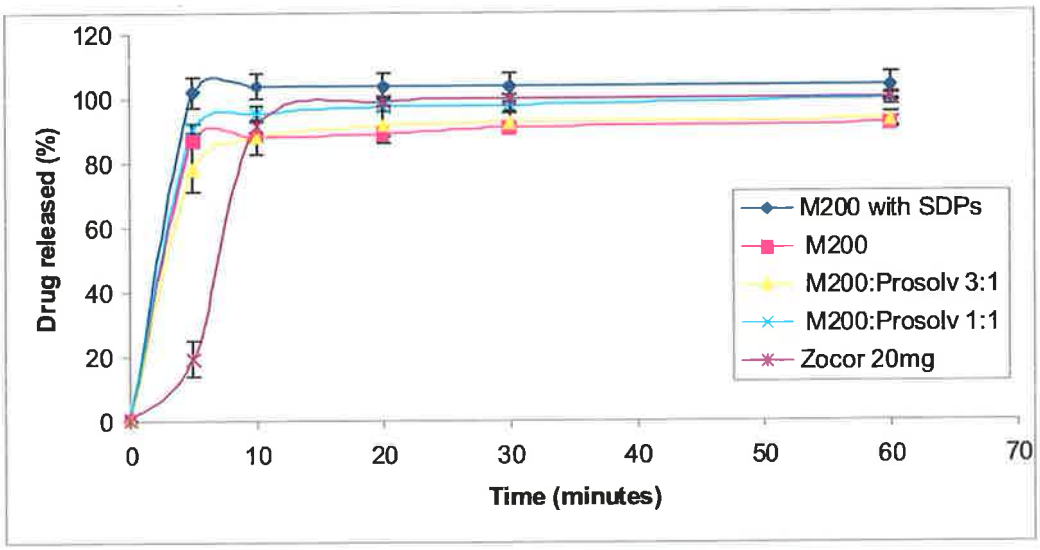

Figure 6.1 Simvastatin release profiles from FDDTs prepared at 49rpm and from 20mg Zocor® tablets.

A one point dissolution testing as per the method outlined in the USP 2007 was used to monitor changes in simvastatin release from the FDDTs after

storage. Dissolution samples were withdrawn at 30 minutes and analysed for simvastatin content. The data in Table 6.6 show that more than 80% of the simvastatin was released in all cases after 30 minutes.

For M200 based FDDTs, an increase in the simvastatin release after 30 minutes was observed from 91.12% at t = 0 to 103.47% at t =3, however then a decrease was observed to 89.41% at t = 6 months. While, for FDDTs containing mannitol:Prosolv in the ratios 3:1 and 1:1, after 3 months, a decrease in the simvastatin release was observed from 92.72 at t=0 to 83.35% at t=3 and 97.95 at t=0 to 90.62% at t=3, respectively.

As per the USP tolerances for the conventional tablets, it says that not less than 75% of the labeled amount of simvastatin is dissolved in 30 minutes.

Table 6.6: Simvastatin release at 30 minutes from FDDTs over 3 - 6 months stability period

Filler	Time point	Drug dissolved (%) at 30mins
Mannitol 200	T = 0	91.12 ± 0.90
Mannitol:Prosolv 3:1		92.72 ± 3.00
Mannitol:Prosolv 1:1		97.95 ± 1.82
Mannitol 200	T = 3	103.47 ± 1.31
Mannitol:Prosolv 3:1		83.35 ± 2.30
Mannitol:Prosolv 1:1		90.62 ± 2.85
Mannitol 200	T = 6	89.41 ± 1.58

6.2. Conclusions

1. Using simvastatin and K-CLSF SDPs or adding Aerosil® as glidant to the M200-KCLSF FDDT formulations resulted in successful tableting at the higher speed of 49rpm, although a higher weight variability was observed for the blend containing the SDP, Aerosil® contributed to enhance the flowability of the M200 FDDT blend, therefore allowing production of tablets with uniform

characteristics at high tableting speeds of 49rpm as opposed to the same blend without Aerosil® which generated tablets with variable characteristics.

2. The addition of increasing amounts of Prosolv® to the M200-KCLSF formulation resulted in formation of tablets with lower weight variability, higher hardness and tensile strength and low DT. DT observed for the Prosolv:M200 FDDTs were below 11 seconds compared to the tablets consisting Manntol 200 where the DT was found to be < 20 seconds.

3. All FDDTs formulated at the higher speed fo 49rpm showed strong mechanical properties as measured by the hardness, tensile strength and friability, thereby making them suitable for handling and conventional packaging.

4. Importantly, M200 with or without Prosolv® showed no stability issues with respect to the tablets characteristics, DT and dissolution time over 3-6months studied. No loss of simvastatin content was observed suggesting little or no degradation over the study period.

5. The dissolution profiles of simvastatin from the FDDTs showed a faster simvastatin release from the FDDTs compared to the Zocor® 20mg tablets. This faster release was related to the fast DT of the FDDTs. As the disintegration step precedes the dissolution step, rapid disintegration could lead to greater degree of drug release, which may result in earlier absorption and enhanced bioavailability of the drug. In addition, the FDDTs containing the SIM SDP was faster with all its simvastatin content released at 5 minutes.

6. The data from this study shows that the simvastatin FDDTs formulations examined have the potential for scale up and commercial manufacture. The in-vivo performance of these formulations may confirm their advantages for faster release and delivery of poorly water soluble actives such as simvastatin.

CHAPTER 7

Conclusions & Future recommendations

7.1 Conclusions

Fast disintegrating dissolving tablets (FDDTs) have gained popularity and acceptance as novel drug delivery systems and have been in great demand as they provide better patient compliance. An ideal FDT has the attribute of fast disintegration in patient's mouth, while maintaining the mechanical integrity to allow the use of conventional packaging. Due to its fast melting in less than a minute in mouth, it does not require any water to swallow and would therefore be beneficial in patients suffering from dysphagia and emesis. In addition, geriatric, pediatric and active people also prefer the convenience that this dosage form offers. Therefore, these dosage forms are rapidly evolving and replacing the existing conventional tablets that require water to be swallowed (Liang and Chen, 2001).

Several technologies have been established in order to produce FDDTs with the desired properties of fast disintegration and good mechanical integrity. The technologies range from freeze drying to tablet moulding to conventional tableting techniques. Although lyophilisation process produces highly porous FDTs contributing to fast disintegration, these tend to produce tablets with too low mechanical strength to allow the use of conventional package and thus require specialized packaging. In addition, freeze drying is an expensive multistep process and requires utmost care during manufacture and handling and therefore requires skilled or trained personnel. Tablet moulding results in FDTs that are weak in mechanical strength and is restricted to actives that are water and heat sensitive.

Conventional tableting techniques have been explored and developed to produce durable FDDTs, however these either require effervescent agents, which make the product moisture sensitive or high levels of disintegrants, which imparts chalky taste in the mouth. These tablets are usually compressed under low compression force, therefore the friability limits for

these tablets are higher i.e. weight loss of NMT 2% is allowed compared to 1% for the conventional tablets.

Direct compression in contrast to granulation is associated with the advantage of comprising comparatively fewer processing steps, and therefore provides economic advantages. This method has also been investigated for formulating FDTs. To enhance the mechanical integrity of the tablets compressed at low compression force, post treatment has been examined where tablets were subjected to temperature and humidity treatment, however this adds another step hence adding complexity (Sandri et al., 2006).

The aim of the present work was to formulate FDTs by simple one - step direct compression tableting. Ideally, the FDDTs produced should be palatable, accompanied by good mechanical strength and rapid disintegration. The influence of various formulation and process variables on the characteristics of the tablets was evaluated.

Placebo tablets were initially prepared. A range of water-soluble or hydrophilic excipients which will enhance the wetting, disintegration and dissolution of tablet dosage form was evaluated. These included selected sugar alcohol based and cellulose based direct compression bases (DCBs) which are either highly water-soluble or water dispersible.

Various fillers including a range of available brands of mannitol, highly water-soluble sorbitol and co-processed fillers such as Ludipress® and Prosolv® were studied. These fillers were different in terms of their particle size. The fillers studied were in order of increasing particle size as Mannogem^{TM}EZ (49.39μm) < Mannitol 200 (94.52μm) < Prosolv® HD90 (127.12μm) < Ludipress® (152.88μm) < Mannitol 300 (193.42μm) < Sorbitol (315.16μm).

Mannogem with the lowest particle size led to the formation of tablets with higher weight variability. The tablets were friable, of low hardness and showed

the lowest disintegration time of 5.67 seconds. Interestingly, sorbitol with the highest particle size produced stronger tablets, however with an accompanying high DT of > 2 minutes. The high hardness of these tablets was related to the binding properties of sorbitol which is used as a liquid binder in solid dose formulations (Swarbrick et al 1991).

The cellulose based filler, Prosolv® was found to have higher tensile strength compared to the sugar alcohol (polyol) based DC filler Mannitol 200. This can be supported by the fact that microcrystalline cellulose at concentrations of 10 to 25%w/w is used as a filler binder and Prosolv® contains 98% of microcrystalline cellulose (Swarbrick et al 1991). Prosolv® based FDTs had lower disintegration times, compared to the Mannitol 200 based tablets. The hydrophilic excipients help to facilitate water entry into the tablet and therefore lead to the fast disintegration of the tablets, while the ability of the co-processed Prosolv® to disperse easily when in contact with water was due to the presence of colloidal silicon dioxide that helps to impart good disintegrant properties to the compact (Cousin et al., 1995, Tobyn et al 1998).

Both, Mannitol 200 (94.52μm) and Prosolv® (127.12μm) were found to generate FDDTs with high mechanical strength and low disintegration times. The friability of these FDDTs was < 1%. It has been reported that the DuraSolv® technology uses a direct compression sugar having particles in the range of 10-80μm. However, the friability limit for these tablets was 2%, as opposed to 1% for the conventional tablets (Khankari et al., 2001).

The fast disintegrant property of the compacts such as tablets is due to the presence of disintegrants, which on contact with aqueous fluid, results in wetting and water uptake into the tablets. This helps break the bonds between the particles of the compact tablet and hence lead to eventual disintegration of the tablets.

Both, Prosolv® and Mannitol 200 were chosen to evaluate the effect of a number of superdisintegrants on the characteristics of the tablets. The various superdisintegrants chosen were different in their disintegration mechanism which include swelling, wicking agent and effervescent agent.

For tablets containing water soluble filler M200 in combination with the disintegrant that works by swelling, Luquasorb® and by wicking action K-CLSF was found to be the most appropriate giving low DT, while for the water insoluble filler, the low DT was observed for the formulation containing Prosolv® in combination with a disintegrant that acts by a swelling accompanied with gelling, SSG.

A combination of M200 and the osmotic agents, sodium citrate and citric acid showed low DTs. The effervescent agent for the preparation of FDDTs has been used by Cima labs for the preparation of its proprietary OraSolv® and DuraSolv®. It provides fast disintegration of the tablet by providing effervescence in contact with saliva, promoting secretion of saliva. In addition, Bonadeo et al., (2000) (Fast melt®) also claimed that the use of only the acid component of the effervescent excipients can lead to fast disintegration of tablets. However, the use of effervescent agents requires controlled conditions of humidity during processing and storage as these excipients are moisture sensitive.
Remeron SolTab® which contains Mirtazepine an antidepressant, is prepared using OraSolv® technology. The tablet diameter is 9.7mm, and the DT reported was 56.6 seconds.

For the superdisintegrant, SSG, the highest disintegration time was observed for the tablets containing Mannitol 200 and the lowest disintegration time for the tablets containing Prosolv® as filler and this was explained as a result of the aqueous solubility of mannitol which competes with SSG for the available aqueous medium.

The trend of DT observed in this study was similar to that reported by Fini et al (2008). These authors reported a DT of > 1 minute for tablets containing mannitol with SSG, while a DT of 32 seconds was obtained for corresponding tablets containing Kollidon® CL.
Okuda et al., (2009) produced orally disintegrating tablets (ODTs) using mannitol spray coated with a suspension of corn starch and crospovidone (2.5:1w/w ratio), showed disintegration time of less than 30 seconds.

The use of a hydrophilic lubricant when compared to the hydrophobic lubricant did not show any significant difference in terms of tablet characteristics, including hardness and DT. Therefore, a conventionally used hydrophobic lubricant, magnesium stearate was used during subsequent studies. Pruss et al., (2003) described fast dissolving tablets prepared from granules of the nanoparticulate active agent blended with mannitol, crospovidone (Plasdone XL; 15%w/w) and, a hydrophilic lubricant, sodium stearyl fumarate and colloidal silicon dioxide. Although the tablets possessed low disintegration times, these were friable.

Various flavours were included in the formulation of the FDDTs to enhance the taste of the tablets. Addition of various flavours caused an insignificant reduction in hardness or increase in the DT. Therefore, it can be concluded that various flavours can be added to the formulation of fast disintegrating tablets, using our formula, without any substantial effect on the characteristics of the tablets.

The studies carried out showed that using a combination of DC filler and superdisintegrants, it was possible to formulate a porous FDDT with attributes of high mechanical strength as well as fast disintegration times of < 40 seconds.

Among the process variables studied, tablet compression force, tablet diameter, tablet shape, and tablet weight were found to influence the

characteristics of the tablets. The effect of increase in the compression force on the characteristics of the tablets was found to be dependent on the diameter of the tablets. In general, an increase in compression force had a higher effect on the hardness and DT of smaller diameter tablets compared to the larger diameter tablets. For 10mm FBE tablets, as the compression force increased from 10 to 20kN, the increase in the DT of tablets was higher, while for the 20mm tablets, the increase in the DT was lower. This was related to higher compression force per unit surface area for the smaller diameter tablets in comparison to the greater diameter tablets.

Interestingly, Jeong et al (2008) reported that as the compression pressure increased for the 500 mg - 12.5mm plane faced tablets, the pores became smaller. When the compression pressure was higher than 2.22kN, the tablet was rendered non-porous, giving disintegration time of more than 1 minute.
The DT for 13mm, 500mg mannitol based FDDTs formulated in our study, compressed at 10kN had a porosity of 24% and the DT was lower at 34 seconds. The friability of these tablets was 0.20%.

The hardness and DT of tablets were directly proportional to the applied compressional force and inversely proportional to tablet diameter for flat faced bevelled (FBE) tablets. For biconvex (BC) tablets, the tablet hardness was proportional to compression force and inversely proportional to the tablet diameter. However, the DT of the BC tablets was found to be independent of the compressional force and tablet diameter.

As the compression force increases from 10 to 20kN, the compression force per unit surface area increases correspondingly for 10mm-20mm FDDTs.

The decrease in tablet hardness with increase in tablet diameter is probably related to the corresponding decrease in compression force per unit surface area. As the tablet diameter increases from 10mm to 13mm to 15 and 20mm, at 10kN, the compression force applied per surface area decreases.

Study of influence of tablet shape showed that, at similar compressional force, the FBE tablets possessed lower hardness, tensile strength and disintegration time compared to the BC tablets. The disintegration time for the FBE tablets was found to be < 49 seconds, while for the BC tablets the DT was > 1 minute, which was related to the lower hardness and higher porosity of the FBE tablets. At 10mm or 13mm, the biconvex tablets have higher density, compared to a density for FBE tablets of diameter 10mm and 13mm, respectively.

An increase in tablet weight by 50% for the 10mm and 13mm tablets, was found to result in a corresponding increase in both, hardness and DT.

In conclusion, the placebo formulations based on Mannitol 200 or Prosolv® in combination with the range of superdisintegrants such as SSG, Luquasorb® or Kollidon CLSF, and compression force 8-10kN for toolings 10-15mm were found to generate tablets with high tensile strength and low DT in the range 2 - 49 seconds. Therefore, these formulations were applied to the model drugs.

The two model drugs, diclofenac sodium and simvastatin, were formulated using M200 and/or Prosolv® filler in combination with the superdisintegrants, SSG, Luquasorb®, K-CLSF and the influence of formulation variables on the characteristics of the FDTs was evaluated.
Diclofenac sodium was included as received, API, in the placebo FDTs. In addition, due to multiple dosage regimens and GI side effects, sustained release dosage form of DFS is preferred over the immediate release form. Diclofenac sodium was microencapsulated using ethylcellulose. The influence of the spray drying parameters on the characteristics of the microparticles was investigated.

Diclofenac sodium microparticles with actual drug loading of 90 - 110% were successfully prepared using conventional one-step spray drying technique at DFS:EC ratio of 1:3.

A decrease in the spray flow rate (SFR) caused a significant increase in the particle size. An improvement in the morphology of the particles and, enhancement in the rheology was observed. Similarly, a decrease in the AAR formed particles with spherical morphology and improvement in the rheology was observed, indicative from a decrease in Carrs index. Also a decrease in FFR caused an improvement in rheology of the microparticles.

The release mechanism of diclofenac sodium from these microparticles showed a high initial burst with >40% of drug released in first 30 minutes followed by sustained release over 7 hours. DFS release was found to be controlled by Fickian diffusion. An increase in spray flow rate caused a decrease in the initial burst release. A similar decrease initial burst release was observed with a decrease in FFR and AAR. The addition of a plasticizer Lutrol® F127 or Tween 20 contributed in further sustaining the drug release profile from the EC microparticles, probably due to formation of tough and flexible ethylcellulose films.

A higher percent of initial burst release of 40 - 72% was expected due to smaller particle size and relatively higher drug loading. Gavini et al (2004) prepared PLGA microspheres of vancomycin using emulsification/spray drying. It was reported that for the microspheres of particle size 11.15 to 10.96μm, a decrease in drug loading from 33% to 25% to 20%w/w, led to a corresponding decrease in the actual drug content from 27.4% to 21.5% to 19.9%, respectively, and an increase in encapsulation efficiency from 84.2% to 86% and 99.5%, respectively. A decrease in initial burst release after 30 minutes was reported from 62% to 56% to 20%.

A phase separation coacervation technique has been used to prepare controlled release formulations of poorly soluble drug diclofenac sodium using ethylcellulose as a polymer by Sajeev et al., (2002). The prepared microcapsules were free flowing and spherical in shape, with the particle size varying from 49.94 - 52.72μm. More than 60% of the drug was released after

20 minutes. The drug release was sustained upto 90 minutes at a DFS:EC ratio of 1:3.

Both an immediate release and modified release FDT of diclofenac sodium were prepared by incorporating DFS API and its sustained release microparticles into M200 FDDT formulations. The inclusion of the DFS API showed tableting issues such as sticking, while the tablets containing DFS microparticles were prepared with a greater ease.

Placebo tablets containing M200 and K-CLSF showed good mechanical strength and low DT. The addition of DFS API generated tablets of lower hardness and higher DT, while for the tablets containing microparticles of DFS, the tablets hardness was relatively higher, but lower than the placebo at, and the DT value was highest amongst all. M200 placebo tablets containing SSG had high hardness and a 3-fold higher DT compared to K-CLSf containing formulation. Addition of DFS API to SSG formulation caused a decrease in hardness and DT. However, addition of microparticles of DFS caused a higher increase in DT at > 1 minute, while the hardness was similar to the formulation containing DFS API.

A palatability study carried out in the dog model showed that 4 out of 6 dogs studied voluntarily accepted the FDDTs, suggesting good palatability of the FDDTs and efficient taste masking of the diclofenac sodium microparticles.

Simvastatin FDDTs using M200 and Prosolv® as filler were formulated. The influence of inclusion of simvastatin and increasing simvastatin load on the characteristics of the tablets was investigated. In comparison to the K-CLSF placebo tablets, incorporation of simvastatin (5%w/w; 10mg/tablet) caused an increase in the DT of tablets. This can be due to a marginal decrease in the porosity of the tablets, as expected. Likewise, for Luquasorb® based tablets, inclusion of simvastatin caused a remarkable increase in the DT of tablets and decrease in the porosity. Increasing the load of simvastatin from 5% to 10%w/w (10mg to 20mg/tablet) did not cause a change in the tablet characteristics.

Overall, it can be said that the Luquasorb® based simvastatin FDDTs had relatively lower hardness and higher DT compared to the tablets containing K-CLSF simvastatin FDDTs.

Yang et al., (2004) reported that when ketoprofen a hydrophobic drug was used, as the drug content in the formulation increases an increase in the disintegration time of ketoprofen FDTs was observed. This was explained as an increase in the wetting time of tablets due to the presence of the hydrophobic drug.

The influence of increase in tablet turret speed on the formulation of simvastatin FDDTs showed an increase in variability in the characteristics of tablets. This was related to the small particle size of simvastatin and its hydrophobic surface. Therefore, two formulation approaches were investigated to overcome this;

1. Simvastatin was spray dried with various hydrophilic superdisintegrant carriers in an attempt to enhance its rheology, in addition to improving wetting and dispersibility of the hydrophobic drug, simvastatin.
2. The conventional method of addition of a glidant, Aerosil®, to the formulation was also evaluated.

The solid dispersions (SDP) prepared using the superdisintegrant carriers, K-CLSF, SSG, calcium silicate, showed increased median particle dimension uniform particle size distribution and enhanced rheological property. The drug content in SDP with CaS or KCLSF was found to be within the acceptable range of 90-110%. Solid state analysis carried out on the SDP (viz DSC, XRD, HSM) confirmed that the simvastatin in the SDPs was in crystalline form.

The KCLSF-SIM SDP in combination with Mannitol 200 was used to formulate simvastatin FDDTs at high tablet turret speed of 49rpm. Mannitol 200 based simvastatin FDDTs were successfully and continuously produced at high tablet turret speed of 49rpm using the solid dispersions of simvastatin with K-CLSF. The FDDTs showed reproducible characteristics.

Inclusion of the Aerosil® as a glidant with fillers such as Mannitol 200 and a combination of mannitol and prosolv at 3:1 and 1:1 also proved to be beneficial in improving the rheology of the blend consisting simvastatin API thus helping in formation of FDDTs with uniform characteristics. FDDTs formulated had high hardness, low friability and a low disintegration time of less than 22 seconds.

The simvastatin content in these tablets was in the optimal range 92 - 104%.

During dissolution studies, FDDTs formulated using SDP of simvastatin showed instantaneous release of all its simvastatin content after 5 minutes showing that formulation of the hydrophobic drug with a hydrophilic disintegrant can result in a fast dispersibility and dissolution of the drug. In comparison, 87.05% of simvastatin was released from the M200 FDDTs containing simvastatin API and Aerosil®. For FDDTs containing a combination of Mannitol 200 and Prosolv® in the ratios of 1:1 and 3:1 and Aerosil®, 90.82 and 78.13% of simvastatin was released after 5 minutes, respectively.

The data shown in this study supports the rationale for an FDDT formulation of simvastatin for a faster simvastatin release which may enhance its in vivo absorption and bioavailability.

The formulation developed in this work showed desirable qualities of high hardness and low DT. Such FDDTs would therefore not require special handling or packaging conditions and can be shipped in conventional low cost packaging and hence would be of advantage in expanding the range of currently available FDDTs to allow for benefit of ease of dose intake and patient compliance with their therapy, resulting in better disease management.

As selected formulations were shown to tablet at higher speed of 49 rpm without processing issues and little or no change in product characteristics, it can be concluded that the formulations developed in this thesis have the potential to be manufactured at an industrial scale at high tablet turret speeds.

The tablets were found to be stable during storage in securitainers under uncontrolled ambient conditions (lab conditions of temperature and humidity). The novelty of this thesis is that it describes a simple formulation to develop FDDTs of low DT (< 20 seconds) and high mechanical strength, by one-step direct compression process. The amount of disintegrants it uses is < 20%w/w and mostly < 5%w/w, therefore no issues of dry and chalky feel would arise as was observed during dry granulation tableting where > 50% of disintegrants were employed. The formulation does not require special humidity conditions during packaging or storage, as reported to require for the Orasolv®, Durasolv®, technology that uses effervescent excipients. In addition, these FDDTs could be packaged using conventional packaging, as opposed to Zydis® and Orasolv® technology that requires specialised packaging. Microparticles of diclofenac sodium and a hydrophobic drug, simvastatin (log P 4.0) were successfully tableted to produce FDDTs of high mechanical strength and DT of < 30 seconds. Simvastatin formulations were later successfully validated during scale-up and stability studies.

7.2 Future recommendations

Future development of this work would involve an investigation of the simvastatin FDDTs in a human pharmacokinetic study to explore its potential for delivering simvastatin with reduced variability. As part of this future clinical study, data generated during the technology transfer, scale up, packaging and packaged stability would allow for further validation of the formulations. Future work should also investigate the effect of increasing drug content (both hydrophobic and hydrophilic API) of the formulations on the characteristics of the FDDTs formed, to understand its application potential.

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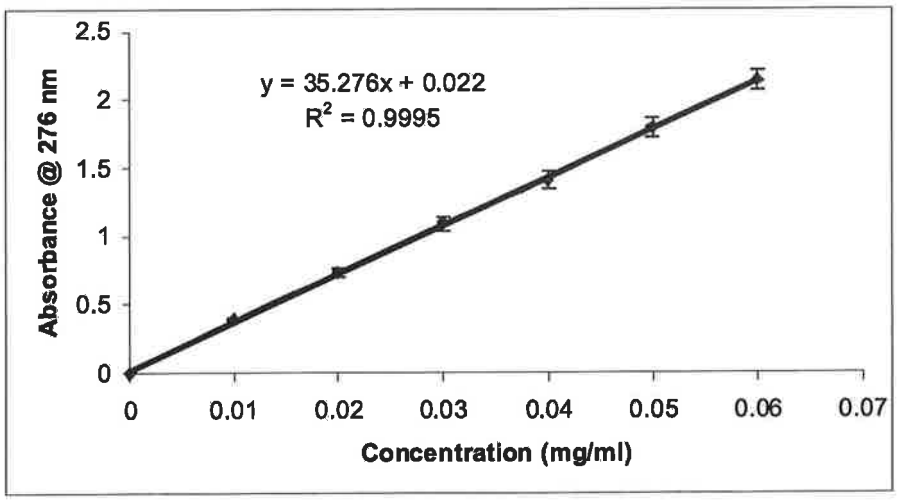
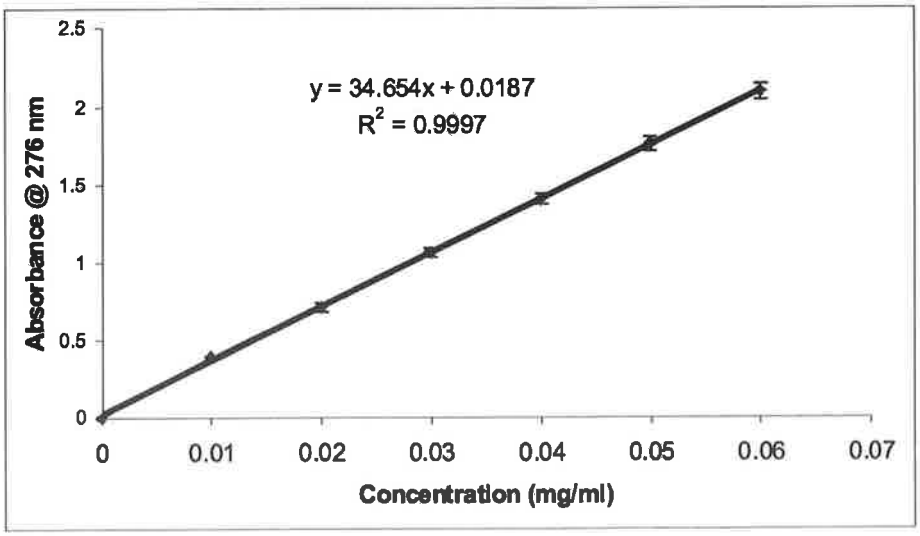
APPENDICES

Appendix 1

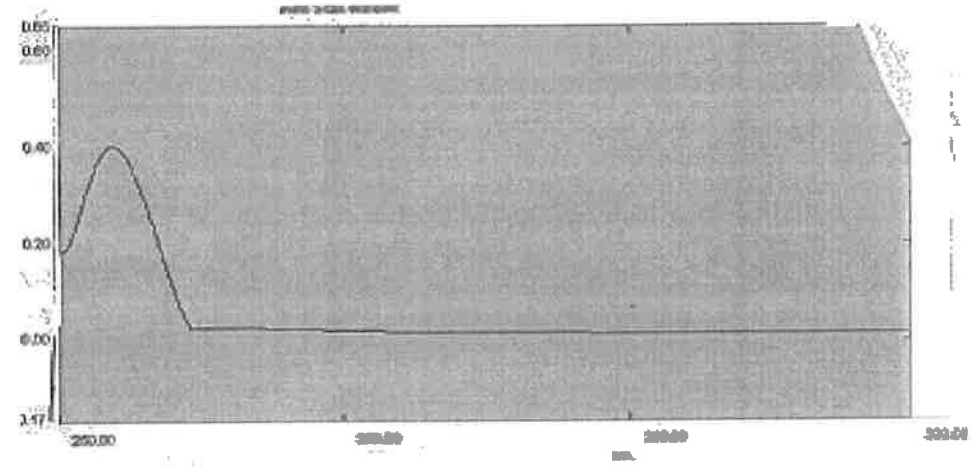
1. Calibration curve for Diclofenac sodium (DFS) at phosphate buffer pH 7.4



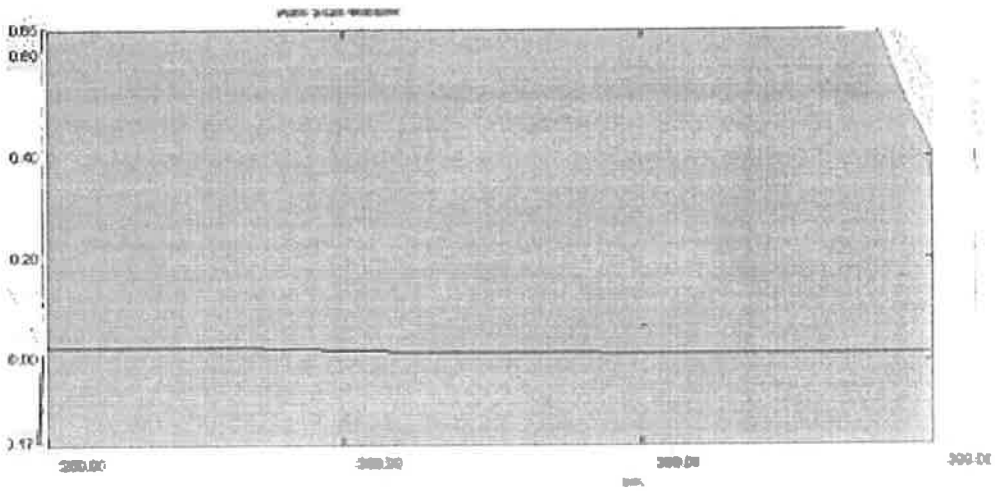
2. Calibration curve for Diclofenac sodium (DFS) at phosphate buffer pH 6.8



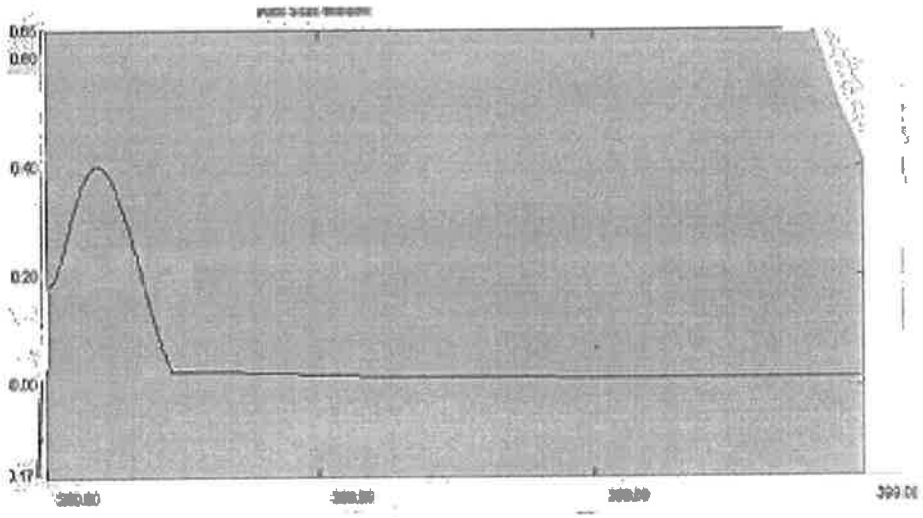
3. UV scan for Diclofenac sodium (DFS)



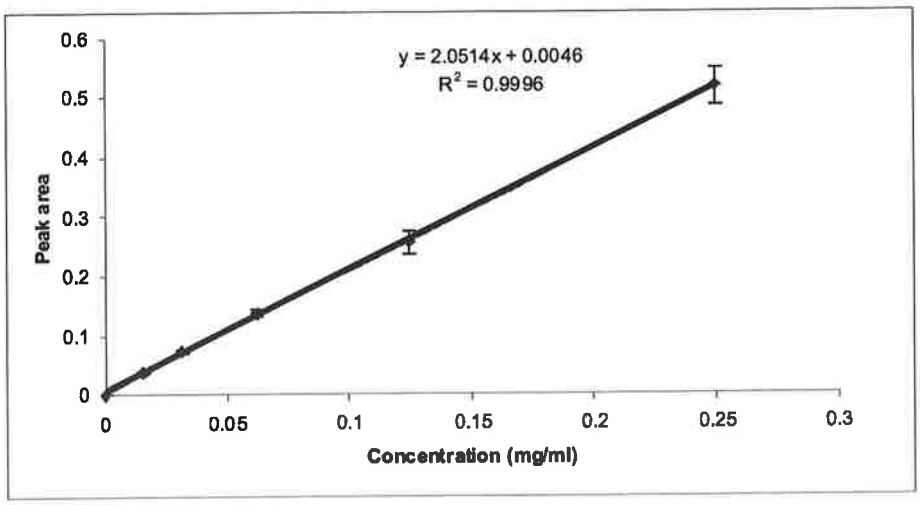
4. UV scan for Ethylcellulose (EC)



5. UV scan for the physical mixtures of Ethylcellulose (EC) with Diclofenac sodium (DFS)



6. Calibration curve for Simvastatin



Appendix 2

1. Influence of the incorporation of various types of filler on the characteristics of 13mm flat faced bevelled edge (FBE) tablets consisting Kollidon CLSF as a superdisintegrant

Ingredients (%w/w)	B086	B079	B084	B085	B112
Mannogem EZ	92.9	-	-	-	-
M200	-	92.9	-	-	-
M300	-	-	92.9	-	-
ludipress	-	-	-	92.9	-
Prosolv HD90*	-	-	-	-	94.5
Kollidon CLSF	5	5	5	5	5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5
Raspberry	0.8	0.8	0.8	0.8	0.8
Mint	0.8	0.8	0.8	0.8	0.8

2. Influence of incorporation of various fillers on the characteristics of 15mm flat faced bevelled edge (FBE) tablets containing a combination of superdisintegrant (SSG) and a dispersible agent (calcium silicate)

Ingredients (%w/w)	B012	B014	B015
M200	79.5	-	-
ludipress	-	79.5	-
Sorbitol	-	-	79.5
Explotab	10	10	10
Calcium silicate	10	10	10
Magnesium stearate	0.5	0.5	0.5

3. Characteristics of 15mm FBE tablets formulated using different disintegrants, compressed at 10kN using Mannitol 200 as filler and magnesium stearate as lubricant

Ingredients (%w/w)	B27	B32	B46	B48	B49	B020
Mannitol 200	81.5	89.5	94.5	89.5	89.5	96.9
CaS	18	-	-	-	-	-
SSG	-	10	-	-	-	-
K-CLSF	-	-	5	-	-	-
Citric acid	-	-	-	10	-	-
Na Citrate	-	-	-	-	10	
L1280	-	-	-	-	-	2
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5

4. Comparison between the two fillers, M200 and prosolv, when used with various superdisintegrants using 13mm FBE tools

Ingredients (%w/w)	B057	B112	B060	B115	B058	B113	B101	B114
M200	94.5	-	97.5	-	89.5	-	79.5	-
Prosolv HD90	-	94.5	-	97.5	-	89.5	-	79.5
K-CLSF	5	5	-	-	-	-	-	-
Luquasorb	-	-	2	2	-	-	-	-
SSG	-	-	-	-	10	10	10	10
CaS	-	-	-	-	-	-	10	10
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

5. Influence of the type of lubricant, hydrophobic or hydrophilic, on the characteristics of 10mm flat faced bevelled edge tablets compressed using M200 as a filler and K-CLSF as a superdisintegrant

Ingredients (%w/w)	001	002	003	004	005	006
M200	94.7	94.5	94.5	94.5	94.5	94.5
K-CLSF	5	5	5	5	5	5
MgS	0.3	0.5	-	-	-	-
Pluriol® E2000	-	-	0.5	-	-	-
Pluriol® E6000	-	-	-	0.5	-	-
Lutrol® F68	-	-	-	-	0.5	-
Lutrol® F127	-	-	-	-	-	0.5

6. Characteristics of tablets formulated using15mm FBE tools, without the use of any flavour and with the use of various flavours

Ingredients (%w/w)	B46	B58	B059	B069	B067	B068
M200	94.5	93.9	93.9	90.5	93.9	91.9
K-CLSF	5	5	5	5	5	5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Raspberry	-	0.6	-	-	-	-
Cherry black	-	-	0.6	-	-	-
Chocolate	-	-	-	4	-	-
Vanilla cream	-	-	-	-	0.6	-
Chocolate +Vanilla cream	-	-	-	-	-	2+0.6

7. Characteristics of Mannitol based FBE tablets formulated at four different tablet diameters i.e. 10mm (B100), 13mm (B101), 15mm (B014) and 20mm (B102) and three levels of compression force i.e. 10kN, 15kN and 20kN

Ingredients (%w/w)	B100	B101	B14	B102
M200	79.5	79.5	79.5	79.5
Explotab	10	10	10	10
Calcium silicate	10	10	10	10
Magnesium stearate	0.5	0.5	0.5	0.5

8. Characteristics of the Mannitol 200 tablets, prepared at two different shapes i.e. FBE and BC tablets, at two different punch size of 10mm (B011 & B100) and 13mm (B008 & B101), and compressed at 10kN compressional force

Ingredients (%w/w)	B011	B100	B008	B101
M200	79.5	79.5	79.5	79.5
Explotab	10	10	10	10
Calcium silicate	10	10	10	10
Magnesium stearate	0.5	0.5	0.5	0.5

9. Characteristics of the Mannitol 200 based, 10mm biconvex, tablets (B011) and 13mm biconvex, tablets (B008), obtained at three different levels of compression force, i.e. 10kN, 15kN and 20kN

Ingredients (%w/w)	B011	B008
M200	79.5	79.5
Explotab	10	10
Calcium silicate	10	10
Magnesium stearate	0.5	0.5

10. Characteristics of the ludipress, 10mm (L1 - B009) and 13mm (L2 - B006), biconvex tablets obtained at three different levels of compression force, i.e. 10kN, 15kN and 20kN

Ingredients (%w/w)	B009	B006
ludipress	79.5	79.5
Explotab	10	10
Calcium silicate	10	10
Magnesium stearate	0.5	0.5

11. Influence of increase in tablet weight on the characteristics of 10mm and 13mm FBE tablets compressed at 10kN

Ingredients (%w/w)	B030	B052
M200	93.4	93.4
K-CLSF	5	5
Magnesium stearate	0.5	0.5
Raspberry	0.6	0.6
Mint	0.5	0.5

12. Blend composition compressed into 15mm tablets for the pre-clinical palatability studies in canine model; magnesium stearate at 0.5%w/w

Formulation	Sample No	Active (% w/w)	Mannitol 200 (% w/w)	Disintegrant (% w/w)	
		SD-DFS	M200	K-CLSF	SSG
1	1*	-	90.5	5	-
	2**	-	93.9	5	-
	3***	-	91.9	5	-
2	4**	-	96.9	-	10
	5*	-	85.5	-	10
	6***	-	86.9	-	10
3	7*	20	70.5	5	-
	8**	20	73.9	5	-

*chocolate 4%w/w, ** raspberry 0.6%w/w, *** chocolate + vanilla 2 + 0.6%w/w

Appendix 3

1. Formulation composition (% w/w) of Mannitol 200 based simvastatin (mg) FDDTs using K-CLSF

Ingredients (% w/w)	B036	B040	B041	B029	B042	B043	B030	B044	B045	B071/78	B073/B080	B072/79	B074/B081
Simvastatin	-	5 (10)	10(20)	-	5(10)	10(20)	-	5(10)	10(20)	-	10(30)	-	10(30)
Mannitol 200	94.5	89.5	84.5	91.7	86.9	81.9	92.9	88.4	83.4	91.7	81.7	92.9	82.9
MgS	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
K-CLSF	5	5.0	5.0	5	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Vanilla cream	-	-	-	0.8	0.8	0.8	-	-	-	-	-	-	-
Chocolate	-	-	-	2	2	2	-	-	-	2	2	-	-
Raspberry	-	-	-	-	-	-	0.8	0.8	0.8	-	-	0.8	0.8
Mint	-	-	-	-	-	-	0.8	0.8	0.8	0.8	0.8	0.8	0.8

2. Formulation composition (% w/w) of Mannitol 200 based simvastatin (mg) FDDTs using Luquasorb

Ingredients (% w/w)	B034	B046	B047	B035	B048	B049	B082	B083
Simvastatin	-	5(10)	10(20)	-	5(10)	10(20)	-	10(30)
Mannitol 200	94.7	89.9	84.9	95.9	91.4	86.4	94.7	84.7
Mg Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Luquasorb 1280	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Vanilla cream	0.8	0.8	0.8	-	-	-	-	-
Chocolate	2	2	2	-	-	-	2	2
Raspberry	-	-	-	0.8	0.8	0.8	-	-
Mint	-	-	-	0.8	0.8	0.8	0.8	0.8

3. Formulation composition (% w/w) simvastatin FDDTs prepared using Prosolv SMCC HD90 as filler

Ingredients (% w/w)	B112	B117	B113	B118	B114	B119
Simvastatin	-	6.67(20)	-	6.67(20)	-	6.67(20)
Prosolv SMCC HD90	94.5	86.23	89.5	81.23	79.5	71.23
Kollidon CLSF	5	5	-	-	-	-
Explotab	-	-	10	10	10	10
Calcium silicate	-	-	-	-	10	10
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Vanilla	-	0.8	-	0.8	-	0.8
Raspberry	-	0.8	-	0.8	-	0.8

4. Simvastatin formulations investigated at an increased compression speed

Ingredients (% w/w)	2008/002	2008/001	2008/015
Simvastatin	5.0(10)	6.7(20)	6.7
Mannitol 200	87.9	86.2	43.1
Prosolv HD90	-	-	43.1
Mg Stearate	0.5	0.5	0.5
K-CLSF	5.0	5.0	5.0
Raspberry	0.8	0.8	0.8
Mint	0.8	0.8	0.8

Appendix 4

Formula for various batches utilized for scale-up and stability

Ingredients (% w/w)	2008/039	SIM002	SIM003	SIM004
Simvastatin	-	6.67	6.67	6.67
Spray dried (1:1)	13.34	-	-	-
Spray dried (1:2)	-	-	-	-
Mannitol 200	84.56	85.73	63.923	42.865
Prosolv HD90	-	-	21.308	42.865
Kollidon CLSF	-	5	5.0	5.0
Magnesium stearate	0.5	0.5	0.5	0.5
Aerosil 200	-	0.5	0.5	0.5
Raspberry	0.8	0.8	0.8	0.8
Vanilla	-	0.8	0.8	0.8
Mint	0.8	-	-	-